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S2k Guideline of the German Respiratory Society

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Pharmacological Treatment of Idiopathic Pulmonary Fibrosis (Update) and Progressive Pulmonary Fibroses S2k Guideline of the German Respiratory Society

Jürgen Behr[1], Francesco Bonella[2], Björn Christian Frye[3], Andreas Günther[4], Lars Hagmeyer[5], Jörg Henes[6], Philipp Klemm[7], Dirk Koschel[8], Michael Kreuter[9,10], Gabriela Leuschner[1], Dennis Nowak[11], Antje Prasse[12], Bernd Quadder[13], Helmut Sitter[14], Ulrich Costabel[2]

Correspondence address:

Prof. Dr. med. Jürgen Behr
Department of Medicine V

LMU University Hospital
LMU Munich

Marchioninistr. 15
81377 Munich
Germany
T: +49 89 440075310
E-mail: juergen.behr@med.uni-muenchen.de

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[1] Department of Medicine V, LMU University Hospital, LMU Munich, Comprehensice Pneumology Center Munich, German Center for Lung Research Munich, Germany
[2] Center for interstitial and rare lung diseases, Pneumology Department, Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany
[3] Department for Pneumology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[4] Center for Interstitial and Rare Lung Diseases, University Hospital Giessen Marburg, Giessen, Agaplesion Evangelisches Krankenhaus Mittelhessen, Giessen, Germany
[5] Bethanien Hospital Solingen, Clinic for Pulmonology and Allergology, Center for Sleep Medicine and Respiratory Care, Institute for Pulmonology with the University of Cologne
6 Department for Internal Medicine II (Hematology, Oncology, Rheumatology and Clinical Immunology), University Hospital Tuebingen, Germany

[7] Justus-Liebig-University Giessen, Campus Kerckhoff, Kerckhoff Clinic, Dept. Of Rheumatology and Clinical Immunology, Bad Nauheim, Germany
[8] Fachkrankenhaus Coswig, Lung Center, Coswig, and Medical Department I, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany

[9] Department of Pneumology, Mainz University Medical Center, Mainz, Germany
[10] Department of Pulmonary, Critical Care & Sleep Medicine, Marienhaus Clinic Mainz, Mainz, Germany
[11] Institute and Policlinic for Occupational, Social and Environmental Medicine, omprehensive Pulmonology Center (CPC) Munich, Member of the German Lung Research Center, Munic, Germany

[12] Department of Pulmonology and Infectiology, Hannover Medical School, German DZL BREATH and Fibrosis Research Department, Fraunhofer ITEM, Hannover, Germany
[13] German Sarcoidosis Association, Germany
14 Institute for Surgical Research, Philipps University Marburg, Germany

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1. Preamble: Definitions: IPF; PPF (PF-ILD)

Interstitial lung diseases (ILD) are characterized by a variable degree of inflammatory and fibrotic changes within the alveolar space and distal airways (bronchioles) [1]. An inverse correlation exists between the extent of fibrosis and the possibility that an ILD is reversible. While the acute (inflammatory) type of extrinsic allergic alveolitis may resolve without sequelae (restitutio ad integrum), IPF is the prototypic fibrotic ILD with a progressive course, leading to an irreversible and progressive fibrosis of the lung parenchyma. Figure 1 provides an overview of the major disease types and the proportion of progressive fibrotic ILD (PF-ILD) [2].

Diagnostic guidelines are available for the accurate diagnosis of IPF [3] [4]. In addition, it has been demonstrated multiple times that the diagnosis of IPF per se is associated with a progressive fibrotic process and high mortality in the majority of cases, without such progression necessarily being recognizable at the time of diagnosis. The progression of IPF manifests as a worsening of respiratory symptoms, concomitant decline in lung function, and progressive remodeling of healthy lung tissue to fibrotic scar tissue, as seen in high-resolution computed tomography (HRCT) imaging. These findings have led to the approval of two drugs—nintedanib and pirfenidone—for the treatment of IPF because they reduce progression, as measured by a decline in forced vital capacity (FVC). The situation is less obvious in other ILDs with a relevant inflammatory component, where a progressive fibrotic phenotype often only develops during the course of the disease. Observational studies demonstrated that, on average, 18%–32% of ILDs transition to a progressive fibrotic disease (PF-ILD) [5] [6] [7] [8] [9] [10]. The fibrotic component of PF-ILD has pathobiological similarities with IPF and also responds favorably to antifibrotic therapy. This has so far been confirmed by studies and a meta-analysis for the antifibrotic drug nintedanib, which was approved for the treatment of PF-ILD on this basis [11] [12]. Although two randomized, controlled trials and their meta-analysis show that the antifibrotic effect of pirfenidone slows disease progression, these studies were flawed due to technical problems or insufficient sample size [13] [14] [1]. Pirfenidone is currently not approved for use in patients with PF-ILD or progressive pulmonary fibrosis (PPF), respectively. Specific clinical criteria were used in the respective pivotal studies to define disease progression and determine the presence of PF-ILD. In the studies of nintedanib, at least one of the following criteria had to be met at the time of inclusion in the study [11]:

1. FVC relative decline ≥10% predicted within 24 months
2. FVC relative decline ≥5% to <10% predicted and worsening respiratory symptoms within 24 months
3. FVC relative decline ≥5% to <10% predicted and increased signs of fibrosis in HRCT within 24 months
4. Increase in signs of fibrosis in HRCT and worsening respiratory symptoms within 24 months

The following criteria were used in the pirfenidone studies to determine the PF-ILD phenotype [13] [14]:

1. FVC absolute decline ≥5% predicted per year, extrapolated based on at least three measurements within 6–24 months [13]
2. FVC absolute decline >5% predicted within 6 months [14]
3. Significant worsening of respiratory symptoms within 6 months not explained by cardiovascular or other causes [14]

Other criteria for determining progression and, thus, the PF-ILD phenotype were used in some publications:

- FVC or DLco absolute decline ≥10% predicted (FVC) or ≥15% predicted (DLco) within 24 months [15]
- Relative FVC deterioration ≥5% and DLco decline ≥15% within 24 months [16]

In addition to the criteria described above, the following findings and clinical events may also indicate progression of the fibrotic ILD, provided that other causes have been excluded [17]:

1. Deteroration of oxygenation and initiation of long-term oxygen supplementation during exercise or at rest according to the current Guideline for Long-Term Oxygen Therapy [18].
2. Hospitalization for worsening respiratory symptoms or acute ILD exacerbation
3. Deterioration in the distance walked in the 6-minute walk test
4. Decrease in minimum oxygen saturation during 6-minute walk test

While a minimum observation period of 6 months was required in the RELIEF study, no other study or recommendation has addressed the question of the minimum observation time required to detect progression [13]. Pretreatment according to the standard of care was recommended but there was no strict requirement for any specific antiinflammatory therapy for inclusion in these studies.

The current international ATS/ERS/JRS/ALAT clinical practice guideline introduces the term “progressive pulmonary fibrosis” (PPF) to replace the previously used term of “PF-ILD”, and defines progression as follows [2]:

At least two of the following three key criteria occurring within the past year:

1. Worsening respiratory symptoms
2. Physiological evidence of disease progression based on lung function (either of the following):
   - Absolute decline in FVC ≥5% predicted
   - Absolute decline in DLco (corrected for Hb) ≥10% predicted
3. Radiological evidence of disease progression (one or more of the following):
   - Increased extent or severity of traction bronchiectasis and bronchiolectasis
   - New ground-glass opacity with traction bronchiectasis
   - New fine reticulation
   - Increased extent or coarseness of reticular abnormality
   - New or increased honeycombing
   - Increased lobar volume loss

It is critical to exclude alternative causes of worsening of respiratory symptoms, lung function or radiological findings, before the above criteria can be applied as evidence of disease progression in terms of a PPF. This is particularly true for the DLco, which is influenced by a variety of factors, including non-pulmonary ones [2].
The German guideline committee supports the proposed term of "progressive pulmonary fibrosis" (PPF), highlighting that it should be seen as synonymous with the previously used term "PF-ILD", which was also used in the EMA approval document. The German guideline committee considers the definition of progression proposed by the international guideline as too narrow, in particular because important clinical indicators of progression are ignored and some patients may not be able to undergo lung function testing to satisfy the functional criteria, e.g. following an exacerbation, even though a progression is obvious in this case. This might lead to the exclusion of relevant patient groups from beneficial antifibrotic treatment as they will no longer be able to meet the progression criteria.
From the guideline committee's point of view, the following requirements shall be met to initiate an antifibrotic therapy in PPF patients:

1. Fibrotic ILD affecting at least 10% of the lung parenchyma on HRCT imaging.
2. Signs of progression—clinical, functional or radiomorphological deterioration— must be present for a reasonable period of time within a 24-month period. Adopted from the INBUILD pivotal trial [11], the following criteria apply as a general guideline:

either

- an FVC relative decline ≥10%

or Evidence of at least two of the following criteria:

1. Worsening respiratory symptoms
2. FVC relative decline ≥5% predicted
3. Increase in signs of fibrosis on HRCT *****
4. DLco absolute decline ≥15% predicted (DLco)
5. Initiation of long-term oxygen supplementation during exercise or at rest or permanent increase in the oxygen flow of an ongoing long-term oxygen supplementation therapy by at least 1 l/min according to the current Guideline for Long-Term Oxygen Therapy [18].
6. Hospitalization in case of worsening respiratory difficulties or acute ILD exacerbation
7. Decrease in the distance walked in the 6-minute walk test by ≥50m or 20% and/or drop in minimum oxygen saturation during the 6-minute walk test by >5% and below 88% absolute on room air, or ongoing oxygen supplementation at a steady flow rate

***** Hallmarks of the radiologic pattern of fibrosis are:

- Increase in the extent or severity of traction bronchiectasis and bronchiolectasis
- New ground-glass opacity with traction bronchiectasis
- New fine reticulation
- Increased coarseness of reticular abnormality
- New or increased honeycombing
- Increased lobar volume loss

From the guideline committee's point of view, this proposal amalgamates the criteria successfully used in studies and clinically reasonable criteria, without excluding a patient group. In addition, the requirement that at least 10% of the lung parenchyma is affected by fibrotic remodeling increases the probability of progression. The guideline committee also emphasizes that each of these criteria is only valid and can therefore be used as an indicator of progressive fibrosis, if other causes for the deterioration have been rigorously excluded. Causes of clinical deterioration to be ruled out include, in particular, are: left heart failure with pulmonary vascular congestion, developing pulmonary hypertension, overhydration due to heart or kidney failure, and infections.

While the approval of nintedanib and pirfenidone for the treatment of IPF is a regular, diagnosis-based approval, the approval of nintedanib for the treatment of PPF is not an approval for the treatment of a specific disease, but rather for a specific clinical progressive behavior that manifests with a variety of underlying diseases. It is therefore important to note that, in addition to the progression criteria, the presence of a fibrotic ILD needs to be confirmed based on CT morphology using an adequate thin-slice HRCT scan, or based on histological evidence (if available). Reliable radiological criteria of pulmonary fibrosis are honeycombing and traction bronchiectasis or bronchiolectasis; reticulation is also an indicator of fibrosis, especially if quite extensive and subpleural-predominant [3] [4].

All statements regarding the medical therapy made in this guideline refer either to patients diagnosed with IPF based on current guideline criteria in the context of a multidisciplinary team discussion (MDD) [4] or, in the case of PPF, to patients with a fibrotic ILD affecting at least 10% of the lung parenchyma, with signs of progression as per the criteria specified above. An ILD multidisciplinary team discussion (ILD Board) is the gold-standard for diagnosing PPF.

The ILD multidisciplinary team discussion (ILD Board) therefore plays a central role both in diagnosing the condition and in determining progression and, thus, the therapy indication. This requires, at a very minimum, the consultation of a pulmonologist experienced in ILD and of a radiologist with appropriate ILD expertise. If histological findings are available, a pulmonary pathologist shall be consulted as well [3]. Other optional members of an ILD multidisciplinary team are rheumatologists, thoracic surgeons, physiotherapists, dietitians, and palliative care physicians.

Interstitial lung abnormalities (ILA), defined as incidental findings of abnormalities affecting >5% of the lung parenchyma in the upper, mid, and lower lung zones in otherwise asymptomatic individuals, deserve specific consideration and are not included in this gudieline [19]. Please refer to the relevant position paper from the Fleischner Society for information on their management [19].

2. Discussion and appraisal of different pharmacological approaches

2.1. Shall IPF patients be treated with an antifibrotic drug?

R1	Recommendation
⇑⇑	IPF patients shall be treated with one of the two currently approved antifibrotic drugs, nintedanib or pirfenidone.
	Consensus strength: 100%

2.1.1. Shall IPF patients be treated with nintedanib?
Nintedanib is a tyrosine kinase inhibitor blocking in particular the signaling cascade of the vascular endothelial growth factor (VEGF), the fibroblast growth factor (FGF) and the platelet-derived growth factor (PDGF) receptors.

The recommendation provided in the latest 2017 update to the S2k guideline on the pharmacological treatment of IPF states as follows: "IPF patients shall be treated with nintedanib" [20]. In the meantime, antifibrotic treatment has become the "standard of care" for IPF patients. The efficacy of nintedanib therapy was demonstrated in several studies and further confirmed in real world populations.

Before receiving approval, nintedanib was investigated in three clinical trials: one phase II trial (TOMORROW) and two phase-III twin trials (INPULSIS-1 and -2) [21] [22]. All three studies consistently demonstrated that 150mg of nintedanib b.i.d. can reduce the annual FVC decline and, thus, slow disease progression (TOMORROW: Placebo arm
-190ml/year, nintedanib arm: -60ml/year; INPULSIS-1: placebo arm -239.9ml/year, nintedanib arm -114.7ml/year; INPULSIS-2: placebo arm -207.3ml/year, nintedanib arm -113.6ml/year; each p <0.001). In addition, the time to first acute exacerbation was longer in INPULSIS-2 [22]. In the pooled analysis of the two INPULSIS studies, a significant positive effect was found in terms of adjudicated acute exacerbations [22]. In the pooled analysis of TOMORROW, INPULSIS-1 and INPLUSIS-2, the time to first investigator-reported acute exacerbation was also significantly extended [22], and there was a trend in favor of nintedanib in terms of quality of life as assessed by the SGRQ (Saint George Respiratory Questionnaire) [22].

The most common side effects reported in these studies were diarrhea and nausea. Other adverse events, particularly serious adverse events, occurred at a similar rate in the active and in the placebo arm [22].

Data from the TOMORROW extension studies and the INPULSIS studies (INPULSIS-ON) confirmed the positive effect of nintedanib on disease progression in IPF beyond 52 weeks (median treatment time 45 months, maximum treatment time 68 months) with consistent side-effect profiles [23] [24].

Various post-hoc analyses of subgroups of the INPULSIS studies showed no differences in the effect of nintedanib with regard to age, gender, ethnicity, smoking status, baseline FVC, baseline SGRQ, steroid therapy, bronchodilator therapy, antacid co-medication, CT pattern, concomitant emphysema and comorbidities [25] [26] [27] [28] [29] [30]. In a pooled analysis of five randomized trials, the positive effect of nintedanib on FVC decline was comparable for patients <75 and ≥75 years of age as well as for patients with <5 and ≥5 comorbidities [31]. Additional post-hoc analyses of the INPULSIS studies revealed that more patients in the nintedanib arm than in the placebo arm experienced an improvement or no decline in FVC over the study period (25% versus 9%) [32], and that nintedanib reduced the risk of occurrence of acute exacerbations [33] [34].

The INPULSIS studies excluded patients with severely impaired lung function (FVC ≤50% or DLco ≤30%), while patients with such conditions were included in the INPULSIS-ON study [35] [24] and in the INSTAGE study investigating the effect of nintedanib versus a nintedanib/sildenafil combination therapy over a 24-week period in patients with IPF and severely impaired gas exchange (DLco ≤35%) [36]. In these studies, the effect of nintedanib on FVC decline in patients with advanced lung function impairment was comparable to that seen in the INPULSIS pivotal studies for mild to moderate lung function impairment [36]. Safety and tolerability of nintedanib were similar in both patient groups [37].

Clinical insights from IPF centers in Germany support the positive effects of nintedanib in real-world patients [38]. So-called real world experience reports from various other countries also confirm similar clinical outcomes with the already known side effects profile in patients with more advanced disease stages than in those investigated in the clinical trials [39] [40] [41] [42]. Retrospective studies showed that treatment with nintedanib before lung transplantation is safe in terms of bleeding complications, wound healing and short-term post-procedural survival [43] [44] [45].

With regard to all-cause mortality, the pooled analysis of the INPULSIS studies found a beneficial effect, but statistical significance was only achieved in the on-treatment analysis [11]. Extrapolated pooled data from six clinical trials meanwhile suggest that nintedanib improves the life expectancy of IPF patients [46]. This is also supported by data from Medicare beneficiaries in the USA and from the German INSIGHTS IPF registry as well as the European IPF registry, which indicate that antifibrotic medication may confer a survival benefit [47] [48] [49]. However, the proportion of patients treated with nintedanib or pirfenidone was different, and no difference was seen where comparisons between the two treatment options were made.

The analysis of global pharmacovigilance data sets from 2014 to 2018 showed that the safety profile of nintedanib in IPF patients was no different from that already observed in the clinical trials and as described in the package leaflet [50]. No safety concerns were raised.

From the guideline committee's point of view, the recent post-hoc analyses, the long-term data as well as insights from real-world observations speak for a beneficial and clinically relevant effect of nintedanib on the progression of IPF, with a generally acceptable side effects profile.

2.1.2. Shall IPF patients be treated with pirfenidone?
Pirfenidone is an anti-fibrotic agent and can block the release of pro-fibrotic and pro-inflammatory cytokines [51] as well as reduce collagen synthesis and fibroblast proliferation [52].
The latest 2017 update of the S2k guideline on hharmacological treatment of IPF provided the same recommendation for pirfenidone as for nintedanib: "IPF patients shall be treated with pirfenidone" [20]. The efficacy of pirfenidone was confirmed in several studies as well as in real world settings.

Pirfenidone has been studied in IPF patients in the context of six clinical trials: two phase-II trials, of which one was an open-label [54] and the other one a randomized trial [55], as well as four phase-III trials [56] [57] [58]. While the patients in the phase-III CAPACITY 1 trial were randomized into three groups (high-dose pirfenidone: 2403mg/day; low-dose pirfenidone: 1197mg/day; placebo), the otherwise identically designed CAPACITY 2 study had only two groups (high-dose pirfenidone: 2403mg/day; placebo) [57]. In CAPACITY 1, a significant decline in FVC was seen in the high-dose group versus placebo over a 72-week-period (mean change vs. baseline of -8.0% absolute vs. -12% absolute; p=0.01), while no significant difference was seen in CAPACITY 2 (-9.0% vs. -9.6%; p=0.50). The pooled analysis of the two CAPACITY studies (high-dose versus placebo) revealed significant benefits of pirfenidone in terms of FVC decline, categorical deterioration of FVC >10%, progression-free survival, and distance walked in the 6-minute walk test, but not with regard to all-cause mortality [57]. Patients in the ASCEND study (A Randomized, Double-Blind, Placebo Controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis) were given either pirfenidone (2,403mg/day) or placebo [58]. After 52 weeks of treatment with pirfenidone, the decline in FVC (% predicted) was 41.5% less and the percentage of patients who had died or experienced a decline FVC ≥10% was 47.9% less (p=0.001) than in the placebo group. Treatment with pirfenidone resulted in significant benefits in terms of distance walked in the 6-minute walk test, progression-free survival and reduced mortality numerically, although this difference was not significant (HR 0.55; CI 0.26–1.15; p=0.10) [58]. The pooled analysis of the CAPACITY 1 + 2 and ASCEND studies, including all patients under 2,403mg of pirfenidone versus placebo, demonstrated significant benefits in terms of FVC decline, FVC decline ≥10% or mortality, progression-free survival, 6MWT distance as well as patient-reported dyspnea [59]. The pooled analyses of all three studies revealed a significant benefit of pirfenidone therapy in terms of all-cause mortality, IPF-related all-cause mortality as well as all-cause and IPF-related mortality [58] [60]. The open-label extension studies of ASCEND and CAPACITY (RECAP) revealed no new aspects in terms of the long-term tolerability and safety profile of pirfenidone [61].

The pooled data indicate that nausea, skin rush (including phototoxicity) and anorexia, in particular, are more frequent under treatment with pirfenidone [62] [59].

Various post-hoc subgroup analyses were published for the CAPACITY and ASCEND studies. There were no differences in the effect of the treatment with regard to FVC and the GAP (gender, age, physiology) index at baseline [63]. Patients with severely impaired lung function (FVC <50% and/or DLco <35%) also benefited from the treatment with pirfenidone in terms of FVC decline, all-cause mortality and hospitalization, without a significantly increased risk of adverse events [64]. In addition, the analyses showed that pirfenidone reduces the annualized risk of respiratory-related hospitalization [65]. Another post-hoc analysis of the CAPACITY and ASCEND data found that pirfenidone reduced the multiple occurrences of disease progression events (defined as relative FVC decline ≥10%, absolute decline in distance walked in the 6-minute walk test ≥50m, respiratory-related hospitalization or all-cause death) and death in the year following such progression event [66]. In addition, patients with more advanced disease stages (FVC<80% and/or GAP stage II/III) who were treated with pirfenidone experienced positive effects with regard to patient-reported dyspnea under pirfenidone [67]. A post-hoc analysis of the RECAP extension study revealed that, even in patients with severely impaired lung function (FVC <50% and/or DLco <35%), the FVC decline takes a similar course over an extended period as in patients with less impaired lung function, and that the safety profile is similar [68]. In addition, concomitant antacid therapy was comparable to pirfenidone alone, according to data from the CAPACITY and ASCEND studies [69].
The observations made in the PASSPORT multicenter study, in which real-world IPF patients under pirfenidone were followed for two years, were consistent with the safety profile observed in the clinical trials [70]. Real-world data from Germany also confirm the therapeutic benefit of pirfenidone without the occurrence of new adverse events [71] [72] [73]. Treatment with pirfenidone also appears to be safe before lung transplantation and is not associated with an increased risk of bleeding, delayed wound healing or poorer short-term post-procedural survival [43] [44] [45].
Overall, the treatment with one of the two currently approved antifibrotic drugs seems to improve survival for IPF patients [47] [48] [49]. Data from a small-scale study on 43 patients also demonstrate positive effects of pirfenidone on the cough symptoms in patients with IPF [74].

From the guideline committee's point of view, these studies continue to highlight the beneficial and clinically relevant effect of pirfenidone on disease progression in IPF with a generally acceptable side effects profile.

2.2. Shall IPF patients be treated with antacid medication?

R2	Recommendation
⇓⇓	IFP patients shall not receive antacids to treat pulmonary fibrosis.
	Consensus strength: 100%

An increased prevalence of gastroesophageal reflux (GERD) [75] is seen in IPF patients, and gastroesophageal reflux associated (micro-)aspiratioin may damage the lung parenchyma [76]. A study on a small number of IPF patients suggests that surgical fundoplication may slow the progression of IPF [77] in this context. The extent to which antacid therapy might have a similar effect on IPF progression has not yet been investigated in a prospective, placebo-controlled study. Various post-hoc analyses did not reveal any apparent beneficial effects of antacid therapy in terms of survival or the slowing down of the decline in lung function in patients under antacid therapy [78]. In the pirfenidone and nintedanib studies, neither the placebo nor the active treatment arms provided a positive effect in terms of overall survival or lung function decline in patients treated with additional proton pump inhibitors (PPI) [79] [80] [29]. These post-hoc observations are consistent with analyses from the British healthcare system, where—using a so-called "new user cohort study design"— the effect of ongoing PPI therapy was investigated in over 1800 patients already diagnosed with IPF, and compared to matched IPF patients not treated with PPI [81]. There was no difference in terms of all-cause mortality or hospitalization rate associated with the use of PPI [82].

Based on the study data available to date, there is no value in antacid therapy (such as PPI) for the treatment of IPF. Irrespective thereof, a guideline-directed medical therapy of gastroesophageal reflux disease is clearly indicated for IFP patients.

2.3. Shall IPF patients be treated with N-acetylcysteine?

R3	Recommendation
⇓⇓	IPF patients shall not be treated with N-acetylcysteine.
	Consensus strength: 100%

Since the first studies on the effect of N-acetylcysteine in combination with azathioprine and prednisone or as monotherapy in patients with IPF were conducted [83] [84], in which no convincing effect of N-acetylcysteine on FVC was seen, further studies have investigated the effectiveness of N-acetylcysteine in IPF. While a 2019 meta-analysis describes a positive effect of N-acetylcysteine on FVC [85], reservations remain as, among other factors, the majority of the studies reviewed was insufficiently powered due to small sample size, and investigated a combination therapy of N-acetylcysteine and corticosteroids. The combination of N-acetylcysteine with pirfenidone as one of the drugs currently recommended for the treatment of IPF shows no additional benefit in terms of quality of life or delaying disease progression [86] [87]. The administration of inhaled N-acetylcysteine as add-on to pirfenidone may even be potentially harmful [88]. Of interest are post-hoc analyses of patient cohorts treated with N-acetylcysteine in a study context (including those mentioned above). These analyses show differences in the effects of N-acetylcysteine on lung function depending on TOLLIP genotype [89]. A prospective study, in which this aspect will be investigated, is currently recruiting IPF patients for genotype-stratified treatment with N-acetylcysteine (clinicaltrials.gov; NCT04300920). In addition, another retrospective study suggests that N-acetylcysteine may have a positive effect on the transplant-free survival of patients with ANA-positive pulmonary fibrosis [90].
Based on currently available data, IPF patients shall not be treated with N-acetylcysteine outside controlled clinical trials. It may be possible, however, that IPF-associated genetic polymorphisms and/or phenotypes will be identified in the future, where N-acetylcysteine can have a beneficial effect.

2.4. Shall IPF patients be treated with dual endothelin receptor antagonists (ET-A and ET-B) bosentan or macitentan?

R4	Recommendation
⇓⇓	IPF patients shall not be treated with bosentan or macitentan to treat the fibrosis.
	Consensus strength: 100%

A number of in-vitro and animal study data suggest that the blocking of endothelin receptors may have a positive effect on the progression of the pulmonary fibrosis [91] [92]. The BUILD-1 study of bosentan showed a statistically non-significant reduction in disease progression in the bosentan group, although the primary endpoint (distance walked in the 6-minute walk test) was not met [93]. A consecutive phase-3 trial of bosentan versus placebo (BUILD-3) in a larger IPF patient population showed no effect on a combined primary endpoint incuding lung function and acute exacerbation [94]. Similar negative results were obtained in the MUSIC study, which investigated the effect of macitentan primarily on clinical deterioration and lung function in a population of 178 IPF patients. Treatment with macitentan showed no significant beneficial effect with regard to lung function or clinical deterioration of IPF [95].
A study on the effect of bosentan on the pulmonary hemodynamics of IPF patients could not demonstrate a therapeutic hemodynamic or clinical effect [96].
Based on currently available data, IPF patients shall not be treated with bosentan or macitentan.

2.5. Shall IPF patients be treated with the PDE5 inhibitor sildenafil?

R5	Recommendation
⇓	IPF patients should not be treated with sildenafil to treat the pulmonary fibrosis.
	Consensus strength: 100%

Treatment of IPF with sildenafil was initially tested in two prospective studies with 180 IPF patients who were treated with 3 x 25mg of sildenafil in the larger of the two studies (STEP-IPF study) [97] [98]. The primary endpoint (improvement in the distance walked in the 6-minute walk test) was not met in either study, although some of the secondary endpoints, e.g. oxygenation and patient-reported dyspnea, improved significantly under sildenafil in the STEP-IPF study [97]. A significant effect on distance walked and quality of life was evident in particular in the sub-study of patients with echocardiographic findings of right-ventricular dysfunction [99]. In view of these potential benefits of sildenafil, two large studies investigated the extent to which sildenafil as add-on to an ongoing antifibrotic treatment with nintedanib [36] or pirfenidone [100] might have a positive effect on quality-of-life parameters, distance walked in the 6-minute walk test, as well as lung function. Both studies included mainly patients with severely impaired diffusing capacity (DLco ≤35% and ≤40%, respectively). In addition, only patients with confirmed precapillary hypertension or with echocardiographic signs suggestive of pulmonary hypertension were included in the pirfenidone/sildenafil study [101]. Both study results suggest that the addition of sildenafil to an ongoing antifibrotic treatment is safe. However, the primary endpoint was not reached in either study. The combination of sildenafil and nintedanib did not significantly improve patient-reported dyspnea (measured using specific questionnaires) at week 12 or 24, and there was also no significant difference in the lung function parameters. The only significant difference was that brain natriuretic peptide (BNP) plasma concentrations were lower in the active arm, which may be indicative of lesser myocardial (presumably right-ventricular) strain. A subgroup analysis of patients with or without echocardiographic signs of right- ventricular strain also found no significant difference in terms of quality of life and lung function, although the effect on BNP was stronger in patients with pre-existing right-ventricular strain [102]. The pirfenidone-sildenafil combination therapy over one year also had no significant positive effect on disease progression compared to a pirfenidone monotherapy [100], with disease progression being defined as significant decline in the distance walked in the 6-minute walk test, respiratory hospitalization, or death.
The evidence from available data is not sufficiently robust to support that sildenafil (as monotherapy or as add-on to antifibrotic therapy) would significantly improve relevant endpoints in IPF patients. IPF patients—with or without pre-existing pulmonary hypertension—should not be treated with sildenafil monotherapy or with sildenafil in combination with antifibrotic drugs.

2.6. Shall PPF patients be treated with antiinflammatory agents?
2.6.1. Non-autoimmune PPF

R6	Recommendation
⇑⇑	Non-autoimmune PPF patients shall be treated with antiinflammatory agents if an inflammatory component is suspected to contribute to the progression of pulmonary fibrosis, after other measures such as antigen avoidance or restriction/limitation of exposure have been considered. The therapy shall be determined in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

In most cases of chronic progressive fibrosing interstitial lung disease, progression is triggered by a chronic inflammatory immune response. Prolonged inflammation eventually leads to scarring. Based on these considerations, antiinflammatory therapy is routinely used to treat PPF. The strategy is complicated, however, by the fact that PPF can be caused by different types of inflammatory responses, e.g. by B- or T-cell driven processes. Different antiinflammatory drugs or drug combinations are therefore used based on a patient's specific condition. The underlying inflammatory activity of the PPF varies greatly, also from patient to patient within a specific entity. In addition, inflammatory activity may change as the disease progresses [103], and often tends to get less as the

fibrosis progresses. A retrospective study of patients with chronic fibrotic ILDs (37 iNSIP, 16 iPPFE, 133 unclassifiable IIP) in Japan showed that BAL lymphocytosis was associated with a better prognosis only in patients treated with antiinflammatory drugs, but not when no antiinflammatory agents were not used [104].
Evidence regarding the use of anti-inflammatory therapy in ILDs other than those caused by theumatoid arthritis and collagen vascular systemic diseases is limited, because there are no randomized controlled trials. Nevertheless, anti-inflammatory therapies are routinely used to treat progressive fibrotic ILDs. Even in the INBUILD study, patients with a UIP-like pattern were treated with glucocorticoids (<20mg/day) at baseline in approx. 50% of cases and with other immunomodulators in 18% of cases [103]. The same goes for the RELIEF study on PF-ILD, in which 81% of patients were treated with glucocorticoids and/or other immunomodulators [13]. In a recent international online survey, specialists stated that 25–70% [105] of their PPF patients were not treated with antiinflammatory drugs, especially considering those patients with idiopathic NSIP and unclassifiable ILD [106], where controversial data on the effectiveness of anti-inflammatory therapy exist. In patients with chronic progressive idiopathic NSIP and HP who progress despite steroid monotherapy, azathioprine, mycophenolate mofetil and cyclophosphamide are mostly used as add-on to the steroid therapy, usually in a steroid-sparing intention [107] [108] [109] [110] [111] [112] [113].
The successful use of rituximab was reported in a small number of patients with progressive chronic HP [114]. Additional data from clinical trials on the role of rituximab for the treatment of ILD are to become available in near future (NCT02990286).
When should antiinflammatory therapy be started in non-autoimmune ILD? For patients with chronic HP (cHP), DIP, silicosis and asbestosis, it is necessary to first rule out that the progression of pulmonary fibrosis is related to continued exposure (e.g. triggering antigen, smoking, occupational exposure). With regard to cHP, the risk of progression is higher and the prognosis is poorer if antigen avoidance is not implemented or if the triggering antigen is not known and antigen avoidance therefore not possible [115] [116].
The authors of this guideline use the following parameters to decide for or against the initiation/increase of anti-inflammatory therapy for PPF patients:

1. clinical parameters (e.g. previous response to therapy),
2. HRCT morphology (inflammatory vs. fibrotic),
3. clinical chemistry (e.g. CRP, IL-6, sIL2R),
4. differential cytology of BAL, as applicable, and
5. histology findings.

The decision shall be taken in the context of an ILD multidisciplinary team discussion (ILD Board).
In the study by Yamagata et al., BAL lymphocytosis <15% was an independent negative predictor for response to antiinflammatory therapy. [104]. In a retrospective study of 91 patients with fibrotic HP, BAL lymphocytosis <20% in conjunction with honeycombing on HRCT was found to be corticosteroid refractory [117]. Consequently, a BAL lymphocytosis greater than 20-30 % in the absence of a UIP pattern on HRCT may foster an anti-inflammatory treatment strategy.

2.6.2. Autoimmune PPF

2.6.2.1. Introduction

Autoimmune ILD manifests as a highly heterogeneous group of conditions.
Due to their heterogeneity and the limited data available, the following general rule applies:
As with non-autoimmune PF-ILDs, a multidisciplinary approach with expert input from a rheumatologist is required.
The type of underlying rheumatic disease shall be considered in the decision on the antiinflammatory therapy of choice for the autoimmune ILD, with due consideration of any additional organ involvement. The therapy shall treat the autoimmune ILD as well as any other organ manifestations.
Below is an overview of the evidence available for the various disease types. The recommendations are specified, where possible.

2.6.2.2. Rheumatoid arthritis-associated ILD (RA-ILD)

R7	Recommendation

⇑	Progressive RA-ILD should be treated with antiinflammatory drugs. The therapy shall be chosen in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

RA-ILD affects approx. 10% of RA patients, primarily those who are APCA positive. Smoking, exposure to dust and male sex are risk factors for RA-ILD. In addition, the MUC5b polymorphism described as the main risk factor for IPF is also highly relevant for RA-ILD [118] [119]. The risk factors mentioned are associated in particular with the occurrence of a UIP pattern, which accounts for approx. half of RA-ILD cases and has a significantly higher rate of progression [118].

The evidence base for antiinflammatory therapy in RA-ILD is generally weak. There are no randomized controlled trials, and the available studies rarely consider the underlying HRCT pattern.

Several retrospective studies report a better outcome and response for this therapy in RA-ILD types with no UIP pattern [120]. A large observational study with 2,701 patients [120] and one meta-analysis [121] both conclude that methotrexate therapy is not associated with the occurrence of ILD; on the contrary, it may delay the manifestation of ILD in RA patients. Numerous other drugs are used to treat RA-ILD, e.g. abatacept, tocilizumab, rituximab, cyclophosphamide, mycophenolate and, more recently, Jak inhibitors [122] [122] [123]. A meta-analysis led to the impression that treatment with leflunomide, TNF inhibitors, rituximab or tocilizumab might increase the risk of developing RA-ILD [124]. In the meantime, however, investigators tend to assume that the impression was created because these drugs were often chosen for the treatment of severe cases with pulmonary involvement. A study by the British Society for Rheumatology demonstrated that rituximab is superior to TNF inhibitors for the treatment of patients with RA-ILD [125].

2.6.2.3. Sjögren’s-associated ILD

R8	Recommendation
⇑	Progressive Sjögren's-associated ILD should be treated with antiinflammatory drugs.
	Consensus strength: 100%

R9	Recommendation
⇑⇑	The therapy shall be chosen in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

R10	Recommendation
⇔	If a follicular component or accumulations of secondary lymphoid follicles are detected, B-cell modulation therapy is an option.
	Consensus strength: 100%

ILD can be a rare manifestation in Sjögren's syndrome [126]. However, given the high incidence of the condition and its usually quite slow progression, Sjögren’s-associated ILD is not a rare disease for pulmonologists. Women are most commonly affected by Sjögren's syndrome. The ILD manifestations of Sjögren's syndrome vary greatly and often go along with bronchial involvement [127]. The histology is often characterized by a follicular component, but lymphocytic interstitial pneumonia (LIP) and, more rarely, a definitive UIP pattern and amyloidosis are also seen. No prospective therapy studies focusing on Sjögren's-associated ILD were found [126]. Patients with Sjögren's-associated ILD are commonly subsumed under collagen vascular disease-associated ILDs.

2.6.2.4. Myositis-associated ILD (MA-ILD)

R11	Recommendation
⇑	Progressive MA-ILD should be treated with antiinflammatory therapy. The therapy shall be chosen in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

The spectrum of myositis disorders includes a rare group of heterogeneous conditions with varied prevalence of ILD. Approximately 20–40% of myositis patients develop ILD, and in many cases this is the first manifestation of the disease [128]. Some types of MA-ILD do not go along with a clinically relevant myositis. Specific autoantibodies are often associated with ILD, in particular anti-MDA5, anti-SSA and anti-aminoacyl-tRNA synthetase ("anti-synthetase antibodies": Jo-1, PL-7, PL-12, EJ, OJ, KS, YRS (HA), Zo). MDA-5 associated ILD is a rare disease and has a significantly faster progression and higher mortality rate than the other MA-ILDs [129]. In MA-ILD, the inflammatory component seems to be more significant than the fibrotic component, and antiinflammatory therapy therefore plays an important role.
No randomized controlled trials are currently available on the management of ILD in the context of immune-mediated Myositis. The therapy is based on case studies, case-control studies and (retrospective) cohort studies, and can vary across institutions. An important cornerstone in the management of MA-ILD is the close cooperation between rheumatologists and respiratory physicians. Glucocorticoids (GC) are often used as monotherapy or in combination with cyclophosphamide (CYC), azathioprine (AZA), mycophenolate mofetil (MMF), calcineurin inhibitors (tacrolimus (TAC) as well as cyclosporin A (CsA)) and rituximab (RTX).
In an open-label phase-II study, intravenous CYC was associated with improvement in many patients with MA-ILD [130]. A retrospective study by John Hopkins University investigated MMF and azathioprine in 66 patients. Both agents had a positive effect on the lung function [131]. In a US cohort, most of the 54 patients with MA-ILD stabilized under GC + conventional DMARDS (AZA, MTX or MMF). Non-responders were treated with TAC, and most of them responded to the therapy [132]. A prospective, multicenter study demonstrated the superiority of initial GC + TAC combination therapy over (historical) GC monotherapy in terms of early mortality at 52 weeks and FVC in patients with dermatomyositis/ polymyositis [132]. A randomized, prospective, controlled study of 85 MA-ILD patients investigated GC + TAC vs. GC + CSA therapy. The primary endpoint was the progression-free survival, where the TAC regimen proved to be slightly superior to CSA. FVC improved in both groups [133]. A combination therapy of GC + TAC + i.v. CYC had a positive effect on lung function in 29 patients with MDA5-associated MA-ILD in a prospective, multicenter trial [134]. Likewise, the JAK inhibitor tofacitinib had a positive effect in 18 patients with MDA5-positive ILD [135]. In 5 patients with MDA-5-associated ILD who were refractory with GC+CYC+CSA treatment, tofacitinib was used as add-on therapy. Improved survival was seen, with a higher incidence of infections than in the historical controls [136]. It is important to note that the number of subjects was small. Rituximab also showed promise for the treatment of MDA5-positive ILD in a meta-analysis [136]. Moreover, rituximab led to an improvement or stabilization of ILD in 9 out of 10 patients with anti-synthetase auto-antibody-positive ILD in a prospective setting [137].
No prospective randomized controlled trials on the treatment of MA-ILD were found. Nevertheless, some groups report positive effects of various agents on MA-ILD, suggesting that antiinflammatory therapy should be used to treat these patients. Treatment typically involves a combination of several drugs. Currently available data are insufficient to serve as basis for a definite recommendation regarding the choice of drug (or drug class).

2.6.2.5. Systemic sclerosis-associated interstitial lung disease (SSc-ILD)

R12	Recommendation
⇑	Patients with SSc-ILD should be treated with antiinflammatory drugs.
	Consensus strength: 100%

R13	Recommendation
⇑⇑	The therapy shall be chosen in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

Pulmonary involvement is common in systemic sclerosis (SSc), where it is the leading cause of death [138] [139]. Excellent data are therefore available on antiinflammatory therapy for the treatment of SSc-ILD, without, however, considering the PF-ILD phenotype.
In 2006, Hoyles et. al. demonstrated improved lung function under intravenous cyclophosphamide (CYC) pulse therapy followed by azathioprine in 45 patients with SSc-ILD vs. placebo (treatment period: 1 year), just short of being statistically significant due to insufficient power [140].
In 2006, another randomized placebo-controlled multicenter study (Scleroderma lung study SLS I) demonstrated the efficacy of oral cyclophosphamide (CYC) vs. placebo in 158 SSc patients. CYC showed a moderate improvement in FVC and TLC over a one-year treatment period, in addition to other improvements such as improved skin scores and chest CT findings [141]. After discontinuing the CYC therapy after one year, the improvement in FVC was lost during follow-up by the end of the second year [139]. In the subsequent SLS II study, the same group compared 12 months of oral CYC vs. mycophenolate mofetil (MMF) (target dose 2 x 1.5 g/day) over a 24-month period in 142 patients [142]. A comparable positive effect of both therapies was seen in this study; the therapy improved the FVC in almost 70 % of patients, while MMF was better tolerated. It is important to note that only patients with confirmed ground-glass opacities were randomized in both studies (SLS I and SLS II). The SENSCIS study, in which approximately half of the patients enrolled were treated with MMF, also suggests the efficacy of MMF in the treatment of SSc-ILD [143].
The double-blind, placebo-controlled phase II + III studies of the interleukin-6 antagonist tocilizumab [144] [145] could not show an effect of tocilizumab with regard to the primary endpoint (skin). However, the differences versus placebo in the secondary endpoints regarding the lung of the phase-III trial wereso convincing that tocilizumab was approved by the FDA for the treatment of severe SSc-ILD in 2021.
In 2021, Ebata et al. presented the data of a randomized, double-blind, placebo-controlled study of rituximab (4 x 375 mg/m²) in 56 SSc patients in Japan [146]. Even though the primary endpoint was skin-related, the secondary endpoints showed a significant improvement in FVC vs. placebo. As early as 2018, a phase-II study from India compared i.v. rituximab with i.v. CYC in 60 SSc patients with skin and lung involvement, demonstrating significant superiority of rituximab with regard to FVC after 6 months [147]. Data from the RECITAL trial (NCT01862926), in which patients with CTD-ILD were randomized to rituximab versus CYC, are pending.
For SSc patients with a particularly rapid progression in the first five years of the disease, a total of 3 randomized, controlled studies showed significant superiority of autologous stem cell transplantation (HSCT) vs. CYC pulse therapy in terms of overall survival, although CYC was only given for 12 months [148] [149] [150]. The positive effect on the lungs was confirmed in a prospective non-interventional real-life observational study [151].

2.6.2.6. Mixed connective tissue disease-associated ILD
ILD in mixed-connective tissue disease (MCTD) is similar to SSc-ILD and therefore not discussed separately.

2.7. Shall PPF patients be treated with an antifibrotic drug?
2.7.1. Introduction
This recommendation is based on the latest international guideline on “IDIOPATHIC PULMONARY FIBROSIS (AN UPDATE) and PROGRESSIVE PULMONARY FIBROSIS IN ADULTS: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline” developed by international experts and approved via consensus voting [2].
The German guideline committee supplemented the systematic literature search on which the ATS/ERS/JRS/ALAT is based by literature published since the guideline was drafted. Hence, no other original treatment studies were published. A systematic review including meta-analysis covered controlled randomized trials on adults with idiopathic pulmonary fibrosis (IPF) or non-IPF ILDs. These trials evaluated pirfenidone or nintedanib and included mortality and lung function data (forced vital capacity (FVC)) [152]. The analysis of 13 studies showed similar, significant effects of antifibrotic therapy in IPF and non-IPF PF-ILD on lung function; pooled data also showed a significant effect on mortality, which was, however, not significant in the analysis of the non-IPF studies (risk ratio

0.908 (0.547–1.508), p=0.71). A small (n=21) retrospective analysis supported the use of nintedanib in progressive pleuroparenchymal fibroelastosis [153]. In addition, several published sub-analyses of the INBUILD study support the previous data [154] [155] [156]. These include an investigation into the combination of immunomodulators (prednisone ≤ 20mg/day) and nintedanib vs. placebo in connection with the INBUILD study [103] and showed that the effect of nintedanib on FVC decline and the side effect profile were not affected by the concomitant antiinflammatory therapy.

2.7.2. Shall PPF patients be treated with nintedanib?

R14	Recommendation
⇑⇑	PPF patients shall be treated with nintedanib. Therapy initiation shall be determined in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

Nintedanib is an antifibrotic agent, which—much like pirfenidone—delays disease progression in IPF patients. Nintedanib is an oral tyrosine kinase inhibitor and blocks key pathways of fibrogenesis. This therapy has been recommended for the treatment of IPF in previous guidelines [157].

The question “Shall PPF patients be treated with nintedanib?” was also examined for 8 different types of ILD with a PPF phenotype. Critical outcome measures included mortality and disease progression (change in FVC); important outcome measures included symptoms (changes in the King's Brief Interstitial Lung Disease Questionnaire (K-BILD)) as well as acute exacerbations.

Summary of evidence

The systematic review that informed the recommendation provided in the international guideline was published separately [12]. In summary, the systematic review identified one randomized trial [11] and one post hoc analysis of the study [158]. In this trial (INBUILD) 663 PPF patients were randomized to receive nintedanib or placebo for 52 weeks, while the post-hoc analysis compared the effects of nintedanib vs. placebo in different ILD subtypes vs. PPF. The ILD subtype was determined by the study sites with no prespecified diagnostic criteria having been provided to investigators and without a central review process. It is therefore possible that the diagnostic process varied across institutions.

Disease progression

Across all PPF patients, FVC declined in both the nintedanib and in the placebo arm of the INBUILD trial, but the mean annual decline was significantly less (107ml) in the nintedanib arm. The trial described “progression of ILD” as an adverse event, without defining it in this context; however, nintedanib lowered the risk of such progression by a factor of 2.4. The difference in the annual decline in FVC between the nintedanib and the placebo arm was 128ml/yr in patients with a radiological UIP pattern, and 75.3ml/yr in patients with no radiological UIP pattern [11]. Nintedanib lowered the risk of progression, measured as an adverse event, by a factor of 2.3 in patients with a radiological UIP pattern, while no significant difference was seen in patients without a radiological UIP pattern [11]. The effect of nintedanib versus placebo on reducing the rate of FVC decline (mL/year) was consistent across the five subgroups by ILD diagnosis in the overall population (HP 73·1 [95% CI -8·6 to 154·8]; autoimmune-associated ILD 104·0 [21·1 to 186·9]; idiopathic NSIP 141·6 [46·0 to 237·2]; unclassifiable idiopathic interstitial pneumonia 68·3 [-31·4 to 168·1]; and other ILDs 197·1 [77·6 to 316·7]; p=0·41 for treatment by subgroup by time interaction). There was also no significant difference in terms of progression in the context of an adverse event for any type of ILD. It should be noted that the estimates are based on small subgroup sizes: Autoimmune ILD (n=147), idiopathic NSIP (n=125), fibrotic HP (n=173), other exposure-related ILD (n=39), sarcoidosis (n=12), non-classifiable ILD (n=114), others (n=53) [158].

Mortality

The INBUILD trial found no significant difference in all-cause mortality with regard to the radiological pattern of the PPF [11].

Adverse effects

Observed adverse events were consistent with the data reported in the IPF studies.

Quality of evidence

The general quality of evidence was rated as low. The rating considers the lowest evidence quality rating of the two critical outcomes; the quality of evidence was moderate for disease progression but low for mortality, because it was a single randomized trial and the number of events was small.

The decision of the international of the ATS/ERS/JRS/ALAT Guideline 2022 committee in favor of a conditional recommendation for nintedanib in PPF patients was based on two main reasons:

1. a statistically significant delay of disease progression, measured as the annual FVC decline, and
2. reversibility of AEs after discontinuation of the therapy.

Further data from the INBUILD study that have since been published also show a significant reduction in acute exacerbations [155], and systematic reviews including meta-analysis are available, which consistently reached a favorable assessment [12] [152]. From the German guideline committee's point of view, a strong recommendation is therefore justified.

It should be noted, however, that the effects of the therapy may vary depending on the type of underlying ILD and that the management approach may be based on the underlying ILD in the future. Currently available data are, however, insufficient to support a targeted approach. The international guideline committee therefore recommends research into the efficacy, effectiveness, and adverse effects of nintedanib in patients with PF-ILD for the different ILD subtypes.

2.7.3. Shall PPF patients receive (off-label) treatment with pirfenidone?

R15 ⇑	Recommendation PPF patients should be treated with pirfenidone if antifibrotic therapy with nintedanib was not sufficiently effective or has been discontinued due to side effects.
⇑⇑	A therapy switch shall be determined in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

In addition to the pivotal trials on the effectiveness of pirfenidone in IPF patients [58] [57], pirfenidone has also been studied in PPF patients in two prospective randomized trials. The uILD study [14] included 253 patients with unclassifiable progressive pulmonary fibrosis (PPF) who were treated with placebo or pirfenidone (2,403mg/day) over a 24-week period. The primary study endpoint was the difference in forced vital capacity (FVC) as measured by home spirometry, the secondary endpoints were the differences in FVC, CO diffusion capacity (DLco), and in the 6-minute walk test (6MWT) as measured at the study site. The primary endpoint was negative, as a meaningful analysis was not possible due to considerable variability and implausibility of patient-reported measured data, which were attributable, at least in part, to technical reasons. By contrast, a significantly smaller decline in FVC was seen when measured at the study site, along with a similarly smaller drop in DLco and in the distance walked in the 6-minute walk test (6MWT). In the RELIEF study [13], 127 patients with PPF associated with fibrotic NSIP, chronic HP, autoimmune ILD or asbestos-related pulmonary fibrosis were included and randomized to receive pirfenidone or placebo for a period of one year. The study was terminated early due to slow recruitment, and study results should therefore be interpreted with caution. With regard to the primary study endpoint, the FVC decline seen in patients treated with pirfenidone was still significantly less than in those who received the placebo, and a consistently lesser decline in DLco and 6MWT distance was seen in the active arm. Another randomized prospective study to evaluate the safety and effectiveness of pirfenidone in patients with rheumatoid arthritis-associated ILD (TRAIL-1 study, NCT02808871) was completed, but only the study design has been published to date [159].

Two recent meta-analyses on the efficacy of antifibrotic therapies in IPF and PPF [53] [152] included studies with pirfenidone in addition to those with nintedanib. They show a significantly smaller FVC decline with an almost identical effect size (approx. -31%) for both IPF and PPF, as well as significantly reduced mortality.

Due to insufficient data, no application has yet been submitted for the approval of pirfenidone to treat PPF. However, data available to date suggest that the efficacy of pirfenidone for the treatment of PPF may be similar to that of nintedanib, although both pirfenidone studies have obvious flaws (endpoint, low recruitment). PPF patients should therefore preferably be treated with the approved standard of care (nintedanib). However, if this therapy is not sufficiently effective (e.g. unchanged FVC decline under treatment or >10% per year) or not tolerated, the guideline committee considers the available data on pirfenidone for the treatment of PPF as

sufficiently positive to initiate a second-line, off-label treatment attempt with pirfenidone in these patients, after obtaining health insurance approval for such off-label use.

2.7.4. Treatment of pulmonary fibrosis related to occupational exposure to fibrogenic noxae

Potential occupational causes of ILD need to be carefully identified based on the patient's occupational history, in particular with a view to eliminating ongoing harmful occupational factors and submitting the mandatory report in respect of an alleged occupational disease, which can help avoid risks for other potentially exposed persons.

Types of pulmonary fibrosis due to occupational dust exposure

The surprisingly high percentage of potential occupational causes of a seemingly "idiopathic" pulmonary fibrosis (26%) (Blanc PD et al, 2019) (192) serves as a reminder for us to systematically investigate a patient's occupational history. The "idiopathic" pulmonary fibrosis studies compiled by Blanc et al (2019) excluded asbestosis and silicosis populations But other occupational causes of ILD had not led to differentiated diagnostic classifications other than IPF.

Given the high rate of occupational risk factors in IPF, two mechanisms are possible:

1. failure to identify manifestations of classical pneumoconioses to a relevant extent, or/and
2. occupational exposure to vapors/gas/dust/smoke can trigger the development of IPF without classic pneumoconiosis.

This raises the question of the extent to which this may have been caused by long-term "low-level" exposure or potential exposure peaks. The latter has not yet been addressed by the German Occupational Safety and Health Act. Action in this regard is necessary.

Park et al (2021) conducted a systematic review including meta-analysis of case-control studies for occupational and environmental risk factors, looking to identify occupational risk factors of IPF [193]. 12 studies out of 2,490 references were included. The following significantly increased odds ratios were identified:

- metal dust: OR = 1.83 (95% CI; 1,15–2,91)
- wood dust: OR = 1.62 (95% CI; 1,04–2,53)
- pesticide use: OR = 2.07 (95% CI, 1,24–3,45)
- working in agriculture; OR = 1.88 (95% CI; 1.17–3.04)

An additional factor is "smoker status"; OR = 1.39 (95% CI; 1.01–1.91).

The systematic review with meta-analysis by Park et al. (2021) [193] did not include a major 2020 Australian case-control study: Abramson et al (2020) recruited 503 patients with IPF and 902 controls. They identified the following risk factors [194]:

- positive family history for IPF: OR=12.6 (95% CI 6,52–24,2)
- occupational exposure to second-hand smoke: OR=2.1 (95% CI 1,2–3,7)
- occupational exposure to dust: OR=1.38 (95% CI 1,04–1,82)
- occupational exposure to asbestos: OR=1.57 (95% CI 1,15–2,15)

"Have you ever smoked?" was included as a factor with an OR = 2.2 (95% CI 1.74–2.70).

The authors concluded that the burden of IPF could be reduced by intensified tobacco control, occupational dust control measures and elimination of asbestos at work [194].

(Please note: It is well-known that asbestosis can also exhibit a UIP pattern. In the absence of bridging phenomena such as pleural plaques and a history of relatively low asbestos exposure, it often presents a problem for the expert opinion if the level of cumulative asbestos exposure is not deemed sufficient for asbestosis while the presentation of a UIP pattern is not regarded as "typical of asbestosis").

From a pragmatic point of view, nothing speaks against treating types of IPF manifesting after occupational exposure to dust that are not yet reflected in the German list of occupational diseases, as IPF not related to occupational exposure. These pathologies are also covered by the indications of pirfenidone ("treatment of mild to moderate idiopathic pulmonary fibrosis (IPF)") and nintedanib ("treatment of idiopathic pulmonary fibrosis (IPF)", "treatment of other progressive fibrotic interstitial lung diseases (ILDs)").

Non-IPF condition as a result of occupational dust exposure

Nintedanib slows disease progression in patients with progressive pulmonary fibrosis other than IPF [11]. For pirfenidone, two phase-2 studies of unclassifiable pulmonary fibrosis and progressive non-IPF pulmonary fibrosis

demonstrated that pirfenidone slows the rate of FVC decline [13] [14]. The study by Behr et al. (2021) included three asbestosis patients [13].
In a 24-week phase-1 prospective observational study of 10 asbestosis patients with progressive lung function decline, Miedema et al. (2022) investigated the safety and tolerability of pirfenidone 801mg 3x/day [194]. While home spirometry showed a decline in FVC in the 12 weeks before starting pirfenidone, it did not decline further during the 24-week treatment period, but the differences were not statistically significant [195].
In the INBUILD study, 332 patients with fibrotic non-IPF lung disease were treated with nintedanib over 16 ± 7 months and compared to a control group of 331 patients [11]. Both in the overall cohort and in the UIP pattern subgroup (n=206 patients treated with nintedanib and n = 206 patients treated with placebo), the rate of FVC decline was significantly lower in those treated with nintedanib. The rate of pneumoconioses is not explicitly stated.
Bonella et al. (2022) analyzed the effects of nintedanib in fibrotic lung disease in a meta-analysis of four placebo-controlled phase-III trials: INPULSIS-1 and -2 for IPF, SENSCIS for SSc-ILD, and the aforementioned INBUILD study [195]. The authors showed that treatment effects did not vary significantly across disease types. Even if this meta-analysis does not explicitly report or separately analyze data for occupational fibrotic lung diseases, it seems reasonable to apply the same conclusion also to “occupational IPF” and pneumoconiosis [196].
Zeng et al. (2022) analyzed eight controlled studies with a total of 292 pneumoconiosis patients who were followed for at least one year with regard to functional capacity after whole-lung lavage [197]. Despite a search across all languages, only studies written in Chinese were identified. Most of the pneumoconioses were coal miners' pneumoconioses, i.e. mixed pneumoconioses related to exposure to dust. Only two studies were ranked as being of good quality. The description of the quality criteria with regard to lung function findings was largely inadequate. The mean decline in FEV1 and FVC across all studies was less in the intervention group than in the control group after two and four years, and in one study after six years [196]. The longer the follow-up, the greater the heterogeneity across studies. Taken together, the problematic quality of the studies makes it difficult to draw valid conclusions. The extent to which “sub-acute” silicosis in the form of alveolar proteinosis may have been present is not evident.

2.8. Shall patients with fibrotic ILD (incl. IPF) and pulmonary hypertension be treated with inhaled prostanoids?

R16	Recommendation
⇑⇑	IPF/PPF patients with signs of pulmonary hypertension shall be referred to a center with special expertise in the management of PH for further evaluation and therapy initiation, as necessary.
	Consensus strength: 100%

The additional development of precapillary pulmonary hypertension (PH) has a serious impact on the prognosis of IPF patients. Several studies have shown that the development of PH significantly reduces the exercise tolerance and survival rates of IPF patients [160] [161]. Moreover, previous studies showed that inhaled prostaglandin I_2 (PGI_2), an established and approved treatment option for PAH, plays a role in lowering pulmonary vascular pressure or resistance in ILD patients with PH without triggering or amplifying a ventilation-to-perfusion mismatch (V/Q mismatch). There was no further deterioration in the already impaired gas exchange in this patient group [162]. On the contrary, inhalation therapy may even improve the V/Q ratio, as it primarily reaches the well-ventilated areas of the lungs where it improves perfusion.
Based on this preparatory work, the INCREASE study, a prospective randomized trial published in 2021, randomized 326 patients with ILD and FVC <70% predicted as well as precapillary PH, as documented by right heart catheterization, to receive either inhaled treprostinil, a synthetic PGI_2 analogue, 72µg 4 x/day 7 or placebo over a period of 16 weeks [163]. The primary endpoint was the 6MWT distance, secondary endpoints were NT-proBNP levels, clinical deterioration rate, as well as lung function parameters such as FVC. Relevant parameters such as age and sex, percentage of idiopathic interstitial pneumonia or IPF or background therapy with antifibrotics at baseline were comparable in both groups. Treatment with treprostinil was associated with a statistically highly significant increase in the 6MWT distance vs. the placebo arm. The difference in walking distance between the active and the placebo arm was 31.12m, and hence above the minimal clinically important difference (MICD) of 28m for IPF patients [164]. A simultaneous drop in pro-BNP levels and fewer exacerbations of the underlying lung disease were also observed as secondary endpoints. Interestingly, a significant increase in

FVC percent predicted vs. placebo was seen in a post-hoc analysis of the study. This effect was most pronounced in the IPF patient group. In view of the diverse, positive extravascular effects of prostacyclin on the epithelial [165] as well as on the mesenchymal [166] [167] compartment, it is hypothesized that inhaled prostacyclin may also unfold antifibrotic properties in patients with fibrotic lung diseases.
The study by Waxman [163] is the first to demonstrate a clinically relevant effect of a pulmonary vasoactive agent—in this case the PGI_2 analogue Treprostinil—in PH patients with relevant ILD. For further guidance please refer to the recent pulmonary hypertension guideline generated jointly by the the European Society of Cardiology (ESC) and European Respiratory Society (ERS) [199].

3. Basis and objectives of the general recommendations
The following recommendations address common clinically relevant questions for which sufficient scientific evidence is not available to date. The following statements reflect the opinion of the members of the guideline committee.

4. Discussion and general recommendations for antifibrotic therapy in IPF and in PPF
4.1. When should antifibrotic therapy be started?
4.1.1. In IPF

R17	Recommendation
⇑⇑	IPF patients shall be treated with antifibrotics from the time of initial diagnosis.
	Consensus strength: 100%

The consensus-based recommendations of the 2017 S2k guideline on “Pharmacological treatment of IPF (update)” advise prompt antifibrotic therapy of symptomatic patients with a definite IPF diagnosis from the time of diagnosis.
This recommendation to start treatment at the earliest possible time remains unchanged. Therapy initiation at the time of IPF diagnosis aims to slow disease progression as early as possible and improve the prognosis. It is important to note that in the placebo arms of the clinical trials patients with “normal” baseline FVC exhibited a similar magnitude of FVC decline as compared to patients with reduced FVC at baseline. The FVC decline also occurs after only a short observation period. A study in which only IPF patients with FVC >80% participated saw a decline in FVC of 70ml in the placebo group after just 12 weeks [168]. Hence, antifibrotic therapy should be initiated, even if the lung function is within reference range [73] [169] [63] [25] [27].
In special cases (e. g. incidental finding during CT examination or lung resection for other indication) of non-symptomatic
patients with no or only minimal limitation of the pulmonary function. a wait-and-watch approach concerning the initiation of therapy can initially be adopted. Also, prognosis-limiting concomitant diseases (e.g. lung cancer) may be a reason not to initiate an antifibrotic therapy. In any event, the individual therapeutic approach has to be discussed with the patient in an open and understandable manner. Even if a decision is made against an immediate initiation of therapy, the patient
should always be subjected to continuous clinical monitoring and control of pulmonary function (at least every 3 months).

4.1.2. In PPF

R18	Recommendation
⇑⇑	PPF patients shall be started on antifibrotic therapy if other appropriate treatments for the specific diagnosis (e.g. antiinflammatory therapy, exposure avoidance) were not sufficiently effective. The decision regarding the therapy for a specific patient shall be made in the context of an ILD multidisciplinary team discussion (ILD Board).

	Consensus strength: 100%

The PPF phenotype includes a wide range of ILD diagnoses. Most patients with a non-IPF diagnosis do not progress and respond to antiinflammatory therapy or avoidance of exposure, etc. [7] [170]).
Disease progression is therefore usually closely monitored and/or an antiinflammatory therapy is initiated at the time of diagnosis, and, in the case of HP and other exposure-associated conditions (exposure to metal dust, medication, etc.), avoidance of the causative noxae is recommended. Only if, in spite of such measures, the development of the disease is classified as PPF according to the progression criteria defined in the preamble, antifibrotic therapy shall be initiated regardless of HRCT pattern [170] [16]. A retrospective analysis of the disease course may also be conducted.
The question of whether patients with prognostic factors for unfavorable outcomes, e.g. UIP pattern, should be treated with an antifibrotic drug from the time of diagnosis remains unresolved [171] [172]. In the INBUILD study, the FVC decline in patients with UIP pattern tended to be greater in the placebo group and the treatment effect of nintedanib better than in patients with other fibrotic HRCT patterns [11].
For more information on the selection of the antifibrotic therapy for PPF *see chapter 2.7. "Shall PPF patients be treated with antifibrotic therapy?"* and *chapter 4.3. "When should switching antifibrotic drugs be recommended?"*.

4.2. When should antifibrotic therapy be discontinued?

4.2.1. In IPF

R19	Recommendation
⇑⇑	In the light of the high mortality of IPF, an antifibrotic therapy which is well tolerated by the patient shall be continued without limitation or until lung transplantation, possibly including a switching between the two approved drugs.
	Consensus strength 100%

R20	Recommendation
⇑⇑	The antifibrotic treatment shall be discontinued when side effects, in spite of symptomatic therapy, dose reductions or temporary interruptions of treatment, cannot be controlled.
	Consensus strength 100%

R21	Recommendation
⇑⇑	A decision for therapy discontinuation shall be taken together with the patient.
	Consensus strength 100%

In principle, treatment failure or non-tolerable side effects may justify a discontinuation of therapy. There is no standard definition for treatment failure. An acute exacerbation or other acute respiratory deterioration is no reason to discontinue the therapy, as post-hoc analyses have shown that continuing the antifibrotic treatment after an acute event is associated with a survival benefit [65] [33]. Even patients with severe IPF still benefit from antifibrotic therapy [68] [64] [35]. Therefore, an advanced disease stage is also no reason to discontinue the therapy.

There is only limited data on the efficacy of antifibrotic treatment over a period of more than 52–72 weeks, i.e. beyond the treatment period in the placebo-controlled pivotal studies. Additional tolerability and safety data from long-term observational studies and real-life cohorts are now available for both antifibrotic drugs. The open-label extension of the ASCEND and CAPACITY (RECAP) trials (mean treatment period 122 weeks, maximum treatment period 349 weeks) and of the phase-IV study (PASSPORT) (real-world IPF patients) revealed no new aspects for pirfenidone in terms of long-term tolerability and safety profile [61] [70]. In addition, long-term analyses of 1,299 patients from 5 clinical trials indicate that pirfenidone is also well tolerated over an extended period of up to 9.9 years (median: 1.7 years) [62]. The open-label extension of TOMORROW (nintedanib) demonstrated that the efficacy of nintedanib and the tolerability was maintained over 52 weeks (median treatment period 28 months, maximum treatment period 86 months) [173]. The long-term observational study of nintedanib (INPULSIS-ON) confirmed the positive effect on disease progression (mean treatment period 45 weeks, maximum treatment period 68 months) with a consistent side effects profile [24]. Real-life data from Medicare patients in the USA, from the German INSIGHTS-IPF registry and the European IPF registry suggest that antifibrotic treatment can improve survival [49] [48] [47].

4.2.2. In PPF

R22	Recommendation
⇑⇑	An antifibrotic therapy which is well tolerated by the patient shall be continued without limitation or until lung transplantation, possibly including a switching between the two available antifibrotic drugs or participation in a clinical trial.
	Consensus strength 100%

R23	Recommendation
⇑⇑	The antifibrotic treatment shall be discontinued when side effects, in spite of symptomatic therapy, dose reductions or temporary interruptions of treatment, cannot be controlled.
	Consensus strength 100%

R24	Recommendation
⇑⇑	Shared decision-making with the patient shall be the basis for discontinuation of therapy.
	Consensus strength 100%

Unlike IPF, no robust data from long-term follow-up of studies, registry studies or real-world populations are available for the treatment of PPF with antifibrotic therapy. Unlike IPF, however, the rate of progression in PPF patients is often known before starting the therapy. This information can therefore be considered in deciding on the discontinuation of a therapy due to treatment failure. If the treatment seems to have no beneficial effect on disease progression over a treatment period of 6–12 months, the termination of the therapy may be considered, after switching antifibrotic drugs, as applicable. (See chapter 4.3. "*When should switching antifibrotic drugs be recommended?*").

4.3. When should switching antifibrotic drugs be recommended?

4.3.1. In IPF

R25	Recommendation
⇑⇑	Antifibrotic therapy shall be switched if IPF patients experience uncontrollable side effects under the current antifibrotic treatment.
	Consensus strength: 100%

R26	Recommendation
⇔	IPF patients whose pulmonary fibrosis has progressed despite several months of antifibrotic treatment may be considered for a therapy switch following thorough risk-benefit assessment.
	Consensus strength: 100%

R27	Recommendation
⇑⇑	Any change in therapy shall be decided in the context of an ILD multidisciplinary team discussion (ILD Board). The option of participating in a clinical trial shall also be considered in this case.
	Consensus strength: 100%

IPF patient cohorts who switched antifibrotic drugs were analyzed in several retrospective studies [38] [174] [40] [175] [176].

A retrospective multicenter study analyzed 62 IPF patients treated with nintedanib, of which 48 patients had previously been treated with pirfenidone. The reasons for switching were pirfenidone intolerance (56%) or disease progression (44%). In this analysis, progression was defined as FVC decline (% pred) >5% within 6 months or FVC decline (% pred) <5% with simultaneous worsening of symptoms or radiological findings [38]. Suzuki et al. analyzed a collective of 262 IPF patients treated with antifibrotics [174]. 37 patients (14%) switched the therapy (pirfenidone to nintedanib n = 29; nintedanib to pirfenidone n = 8) (46% due to progression, 46% due to side effects of antifibrotics, 8% due to first diagnosis of lung cancer, vasospastic angina or at the patient's explicit request). In patients classified as exhibiting progression, the median FVC decline (% predicted) was 14.0% (5.1–22.2) within a median period of 29.9 (24.2–41.6) months before being started on the second-line antifibrotic therapy. Brunnemer et al. studied 64 IPF patients treated with nintedanib [40]. 30 patients had previously been treated with pirfenidone; the reasons for switching to nintedanib were adverse events (70%) and disease progression of IPF under pirfenidone (30%). Progression criteria were FVC decline (% pred) ≥5% and/or a deterioration of DLco ≥15% at any time. A smaller case series of 12 patients, who switched from pirfenidone to nintedanib, yielded similar results (side effects n=9; progression n=3) [175].

It is not entirely clear from the above-mentioned studies whether patients progressing on antifibrotic therapy might generally benefit from a switch to the alternative antifibrotic drug. A recently published Canadian registry study assessed 165 IPF patients who had experienced a FVC decline ≥10% within 6 months under antifibrotic therapy. There was no difference in terms of a further lung function decline between those patients whose antifibrotic treatment was switched and those whose antifibrotic treatment was continued. However, patients whose antifibrotic therapy was definitely terminated had a significantly poorer prognosis [177]. Post-hoc subgroup analyses from the pivotal studies had already demonstrated for both antifibrotic drugs that a consistent continuation of the therapy improves the prognosis versus placebo, even if there is a further FVC decline after therapy initiation [178] [179].

4.3.2. In PPF

R28	Recommendation

⇑	If uncontrollable side effects occur or disease progression does not slow under nintedanib in PPF patients, switching to pirfenidone or the option to participate in a clinical trial should be considered.
	Consensus strength: 100%

R29	Recommendation
⇑⇑	Any change of therapy shall be decided in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

There are no published data on switching antifibrotic therapy in PPF patients. It remains unclear if the criteria for disease progression in PPF (see preamble) might also constitute an indication to switch the antifibrotic therapy. If progression does not slow down in spite of antifibrotic treatment, a therapy switch or the option of participating in a clinical treatment trial should be considered.
As with IPF, a change of therapy or the option to participate in a clinical trial should be considered, if side effects cannot be controlled despite symptomatic therapy, dose reductions or temporary treatment interruptions. The respective decision should be made in the context of an ILD multidisciplinary team discussion (ILD Board).
For information on the optimized management of the side effects of antifibrotic therapy, see the relevant literature on this topic [180] [181] [182].

4.4. Is antifibrotic combination therapy an option?

R30	Recommendation
⇓⇓	Outside of controlled clinical trials, IPF or PPF patients shall not be treated with a combination of pirfenidone and nintedanib
	Consensus strength: 100%

Due to the availability of two approved antifibrotic drugs, the question arises if, similar to other diseases (e.g. bronchial asthma, COPD, PAH or lung carcinoma), a combination therapy might be an even more effective treatment approach. The multifactorial and heterogeneous pathogenesis of IPF and the resulting requirement for a drug therapy to target various profibrotic signaling pathways is a rationale to consider combination therapy [183]. However, we do not yet know if the combination of two effective active drugs will result in a synergistic or additive effect or if drug-drug antagonism may emerge, in which the two drugs render each other less potent. A precedence case is the PANORAMA trial in which the combination of pirfenidone + N-acetylcysteine vs. pirfenidone + placebo was investigated, in the context of which not only no positive effect but possibly even a negative effect of using acetylcysteine as add-on to pirfenidone was encountered [86]. Until this day, unexpected drug interactions with unacceptable side effects cannot be ruled out. In a Japanese phase-2 trial, the profile of side effects, tolerability and pharmacokinetics of nintedanib alone and in combination with pirfenidone was investigated in IPF patients. The study revealed a reduction of the maximum plasma levels and the AUC of nintedanib as well as more frequently occurring side effects in the case of co-medication with pirfenidone compared with nintedanib monotherapy [184]. The open-label, randomized INJOURNEY trial primarily investigated the tolerability of pirfenidone as add-on to stable nintedanib treatment [185]. The combination therapy was associated with an increased rate of gastrointestinal side effects, and the plasma concentration of nintedanib alone was similar to that of nintedanib in combination with pirfenidone. The exploratory efficacy analysis showed at least a signal in terms of a smaller FVC decline in the combination arm over the short 12-week study period (D FVC -13.3 ±17.4ml vs. -40.9 ±31.4ml). In an open-label, single-arm phase-IV study over 24 weeks, the administration of nintedanib in addition to stable therapy with pirfenidone was assessed in terms of tolerability and side effects profile [186]. The combination therapy was tolerated by the majority of subjects (73/89) during the follow-up period, and the side effects profile was similar to that of the respective drugs when

used as monotherapy. A small retrospective observational study in Japan analyzed the tolerability of nintedanib or pirfenidone as add-on to a stable antifibrotic therapy. 30.4% of patients discontinued treatment with either one of the two drugs or with both drugs [187]. Controlled trials will be needed to demonstrate that a combination therapy would be more effective than the respective monotherapy while having a similar safety profile, before a pirfenidone + nintedanib combination therapy can be recommended for IPF patients.
Based on the data of the INBUILD study [11], Nintedanib is currently the only approved antifibrotic treatment for PPF. The results of the German RELIEF trial [13] also demonstrate the effectiveness of pirfenidone in the treatment of PPF, but the drug it is not approved for this indication. There are no published data on the efficacy of a nintedanib-pirfenidone combination therapy in PPF. As with IPF patients, an increased rate of side effects should be expected. Controlled trials will be necessary to demonstrate that a combination therapy would be more effective than the respective monotherapy while having a similar safety profile, before a pirfenidone and nintedanib combination therapy can be recommended for PPF patients.

4.5. What are the implications of the differences in the EMA approvals of pirfenidone and nintedanib in IPF?

R31	Recommendation
⇑⇑	For IPF patients, the selection of antifibrotic drug shall be made with due regard to the severity of the disease, the side effects profile, the comorbidities and any co-medication as well as the lifestyle and personal preference of the patient.
	Consensus strength: 100%

Keeping in mind the absence of a head-to-head comparison between nintedanib and pirfenidone, the currently available literature seems not to imply a relevant superiority of either of the two active drugs over the other, so that no recommendation can be made regarding a preferential use. A comparison of the two substances is complicated by the diverse patient cohorts in the respective pivotal trials resulting from the diverse inclusion and exclusion criteria in the CAPACITY, ASCEND and INPULSIS trials [22] [57] [58]. In Germany, nintedanib has been approved for all IPF patients without consideration of the level of severity, whereas pirfenidone has been approved only for the mild and moderate
IPF. As no objective definition exist for the level of severity, the judgment of severity is up to the treating physician— ideally the multidisciplinary team—in consideration of the clinical symptoms, functional limitations, radiomorphological picture and comorbidities [188]. Meanwhile, a post-hoc analysis of the CAPACITY and ASCEND phase-III trial data for pirfenidone in patients with more severe functional pulmonary impairment (FVC <50% predicted or DLco <35% predicted) [64] has been published. Pirfenidone was significantly superior to placebo for the endpoints of all-cause mortality, FVC decline ≥10% predicted or all-cause mortality, and FVC decline ≥10% predicted or all-cause mortality or respiratory-related hospitalization. The premature discontinuation rate due to side effects was not increased. A Korean observational study prospectively investigated the efficacy and tolerability of pirfenidone in 219 patients, 18% of whom had advanced IPF, defined as FVC <50% predicted or DLco <35% predicted [189]. The incidence of side effects was similar, the efficacy remained the same. In a retrospective analysis from Korea, pirfenidone was shown to have a similar efficacy and side effects profile in patients with advanced IPF (defined as FVC <50% predicted or DLco <30% predicted) as in those with non-advanced IPF [190]. In the prospective controlled SP-IPF study, patients with advanced IPF and risk of pulmonary hypertension were treated with pirfenidone and randomized to receive add-on sildenafil 3 x 20mg/day or placebo. This study confirmed the known side effects profile of pirfenidone, no new aspects were identified, in particular no increased frequency or intensity [100]. Overall, the available study results suggest that pirfenidone is also effective for the treatment of advanced IPF and that its side effects profile is comparable to that observed in mild to moderate IPF.. In the mean time based on pooled analysis of six randomized controlled trials pirfenidone has been approved by the European Medicinal Agency (EMA) for the treatment of IPF without severity limitations [200]
200]

4.6. When should antiinflammatorytherapy be discontinued?

R32	Recommendation
⇑	Antiinflammatory therapy shouldl be discontinued in non-autoimmune and autoimmune PPF if progression or complications (especially infections) or uncontrollable side effects occur over an appropriate monitoring period.
	Consensus strength: 100%

R33	Recommendation
⇑⇑	For autoimmune PPF, the activity of the underlying disease as well as extrapulmonary manifestations of the disease shall be included in the considerations to discontinue the therapy. The decision to discontinue the therapy shall be made by interdisciplinary cooperation, e.g. in the context of an ILD multidisciplinary team discussion (ILD Board).
	Consensus strength: 100%

There is no definite answer to the question of when an antiinflammatory therapy should be discontinued in non-autoimmune or autoimmune PPF. It is a complex decision. A variety of aspects need to be considered and the decision must be made on a case-by-case basis. Infection-related complications and/or increase in fibrotic changes, and the development of honeycombing and traction bronchiectasis in particular are important criteria for reducing or even discontinuing of antiinflammatory therapy [170].
A placebo-controlled study in IPF patients demonstrated that antiinflammatory combination therapy using prednisolone and azathioprine led to increased respiratory tract infections, acute exacerbations and poorer survival outcomes [191]. Especially in patients with telomere lengths below the 10th percentile, the above immunosuppressive combination therapy was associated with a high infection-related complication rate and side effects [198]. The data from the INBUILD study show that in both treatment arms patients treated with antiinflammatory drugs at baseline had more respiratory tract infections and bronchitis than those not receiving this therapy [103].
Treatment with antiinflammatory agents should also be discontinued if side effects cannot be controlled despite symptomatic therapy, dose reductions or temporary treatment interruptions.
In addition, the activity of the underlying disease as well as extrapulmonary manifestations need to be considered in autoimmune PPF in order to control and, if necessary, terminate the antiinflammatory therapy.

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References
[1] Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med. 2020. DOI: 10.1056/NEJMra2005230

[2] Raghu G, Remy-Jardin M, Richeldi L et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. American journal of respiratory and critical care medicine 2022. DOI: 10.1164/rccm.202202-0399ST

[3] Raghu G, Remy-Jardin M, Myers JL et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline.American journal of respiratory and critical care medicine 2018. DOI: 10.1164/rccm.201807-1255ST

[4] Behr J, Günther A, Bonella F et al. S2K Guideline for Diagnosis of Idiopathic Pulmonary Fibrosis.Respiration; international review of thoracic diseases 2021. DOI: 10.1159/000512315

[5] Faverio P, Piluso M, De Giacomi F et al. Progressive Fibrosing Interstitial Lung Diseases: Prevalence and Characterization in Two Italian Referral Centers.Respiration; international review of thoracic diseases 2020. DOI: 10.1159/000509556

[6] Guler SA, Winstone TA, Murphy D et al. Does Systemic Sclerosis-associated Interstitial Lung Disease Burn Out? Specific Phenotypes of Disease Progression.Annals of the American Thoracic Society 2018. DOI: 10.1513/AnnalsATS.201806-362OC

[7] Nasser M, Larrieu S, Si-Mohamed S et al. Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study).The European respiratory journal 2021. DOI: 10.1183/13993003.02718-2020

[8] Reiseter S, Molberg Ø, Haydon J et al. Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study.Rheumatology (Oxford, England) 2018. DOI: 10.1093/rheumatology/kex077

[9] Simpson T, Barratt SL, Beirne P et al. The burden of progressive fibrotic interstitial lung disease across the UK.The European respiratory journal 2021. DOI: 10.1183/13993003.00221-2021

[10] Zamora-Legoff JA, Krause ML, Crowson CS at al. Progressive Decline of Lung Function in Rheumatoid Arthritis-Associated Interstitial Lung Disease.Arthritis; rheumatology (Hoboken, N.J.) 2017. DOI: 10.1002/art.39971

[11] Flaherty KR, Wells AU, Cottin V et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. The New England journal of medicine 2019. DOI: 10.1056/NEJMoa1908681

[12] Ghazipura M, Mammen MJ, Herman DD et al. Nintedanib in Progressive Pulmonary Fibrosis: A Systematic Review and Meta-Analysis.Annals of the American Thoracic Society 2022. DOI: 10.1513/AnnalsATS.202103-343OC

[13] Behr J, Prasse A, Kreuter M et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial.The Lancet. Respiratory medicine 2021. DOI: 10.1016/S2213-2600(20)30554-3

[14] Maher TM, Corte TJ, Fischer A et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. The Lancet. Respiratory medicine 2020. DOI: 10.1016/S2213-2600(19)30341-8

[15] Cottin V, Hirani NA, Hotchkin DL et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. European respiratory review: an official journal of the European Respiratory Society 2018. DOI: 10.1183/16000617.0076-2018

[16] George PM, Spagnolo P, Kreuter M et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities.The Lancet. Respiratory medicine 2019. DOI: 10.1016/S2213-2600(20)30355-6

[17] Cottin V. Treatment of progressive fibrosing interstitial lung diseases: a milestone in the management of interstitial lung diseases. European respiratory review: an official journal of the European Respiratory Society 2019. DOI: 10.1183/16000617.0109-2019

[18] Haidl P, Jany B, Geiseler J, Andreas S et al. Guideline for Long-Term Oxygen Therapy - S2k-Guideline Published by the German Respiratory Society. Pneumologie (Stuttgart, Germany) 2020. DOI: 10.1055/a-1252-1492

[19] Hatabu H, Hunninghake GM, Richeldi L et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. The Lancet. Respiratory medicine 2020. DOI: 10.1016/S2213-2600(20)30168-5

[20] Behr J, Günther A, Bonella F et al. German Guideline for Idiopathic Pulmonary Fibrosis - Update on Pharmacological Therapies 2017. Pneumologie (Stuttgart, Germany) 2017. DOI: 10.1055/s-0043-115504

[21] Richeldi L, Costabel U, Selman M et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. The New England journal of medicine 2011. DOI: 10.1056/NEJMoa1103690

[22] Richeldi L, du Bois RM, Raghu G et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. The New England journal of medicine 2014. DOI: 10.1056/NEJMoa1402584

[23] Richeldi L, Cottin V, du Bois RM et al. Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS(®) trials. Respiratory medicine 2016. DOI: 10.1016/j.rmed.2016.02.001

[24] Crestani B, Huggins JT, Kaye M et al. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. The Lancet. Respiratory medicine 2019. DOI: 10.1016/S2213-2600(18)30339-4

[25] Costabel U, Inoue Y, Richeldi L et al. Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across Prespecified Subgroups in INPULSIS.American journal of respiratory and critical care medicine 2016. DOI: 10.1164/rccm.201503-0562OC

[26] Taniguchi H, Xu Z, Azuma A et al. Subgroup analysis of Asian patients in the INPULSIS ® trials of nintedanib in idiopathic pulmonary fibrosis. Respirology (Carlton, Vic.) 2016. DOI: 10.1111/resp.12852

[27] Kolb M, Richeldi L, Behr J et al. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. Thorax 2017. DOI: 10.1136/thoraxjnl-2016-208710

[28] Raghu G, Wells AU, Nicholson AG et al. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria.American journal of respiratory and critical care medicine 2017. DOI: 10.1164/rccm.201602-0402OC

[29] Costabel U, Behr J, Crestani B et al. Anti-acid therapy in idiopathic pulmonary fibrosis: insights from the INPULSIS® trials. Respiratory research 2018. DOI: 10.1186/s12931-018-0866-0

[30] Cottin V, Azuma A, Raghu G et al. Therapeutic effects of nintedanib are not influenced by emphysema in the INPULSIS trials. The European respiratory journal 2019. DOI: 10.1183/13993003.01655-2018

[31] Glaspole I, Bonella F, Bargagli E et al. Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis who are elderly or have comorbidities. Respiratory research 2021. DOI: 10.1186/s12931-021-01695-y

[32] Flaherty KR, Kolb M, Vancheri C et al. Stability or improvement in forced vital capacity with nintedanib in patients with idiopathic pulmonary fibrosis.The European respiratory journal 2018. DOI: 10.1183/13993003.02593-2017

[33] Collard HR, Richeldi L, Kim DS et al. Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. The European respiratory journal 2017. DOI: 10.1183/13993003.01339-2016

[34] Kreuter M, Koegler H, Trampisch M et al. Differing severities of acute exacerbations of idiopathic pulmonary fibrosis (IPF): insights from the INPULSIS® trials. Respiratory research 2019. DOI: 10.1186/s12931-019-1037-7

[35] Wuyts WA, Kolb M, Stowasser S et al. First Data on Efficacy and Safety of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis and Forced Vital Capacity of ≤50 % of Predicted Value. Lung 2016. DOI: 10.1007/s00408-016-9912-1

[36] Kolb M, Raghu G, Wells AU et al. Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis. The New England journal of medicine 2018. DOI: 10.1056/NEJMoa1811737

[37] Richeldi L, Kolb M, Jouneau S et al. Efficacy and safety of nintedanib in patients with advanced idiopathic pulmonary fibrosis. BMC pulmonary medicine 2020. DOI: 10.1186/s12890-019-1030-4

[38] Bonella F, Kreuter M, Hagmeyer L et al. Insights from the German Compassionate Use Program of Nintedanib for the Treatment of Idiopathic Pulmonary Fibrosis.Respiration; international review of thoracic diseases 2016. DOI: 10.1159/000448288

[39] Galli JA, Pandya A, Vega-Olivo M et al. Pirfenidone and nintedanib for pulmonary fibrosis in clinical practice: Tolerability and adverse drug reactions. Respirology (Carlton, Vic.) 2017. DOI: 10.1111/resp.13024

[40] Brunnemer E, Wälscher J, Tenenbaum S et al. Real-World Experience with Nintedanib in Patients with Idiopathic Pulmonary Fibrosis. Respiration; international review of thoracic diseases 2018. DOI: 10.1159/000485933

[41] Tzouvelekis A, Karampitsakos T, Kontou M et al. Safety and efficacy of nintedanib in idiopathic pulmonary fibrosis: A real-life observational study in Greece. Pulmonary pharmacology therapeutics 2018. DOI: 10.1016/j.pupt.2018.01.006

[42] Yoon HY, Park S, Kim DS et al. Efficacy and safety of nintedanib in advanced idiopathic pulmonary fibrosis. Respiratory research 2018. DOI: 10.1186/s12931-018-0907-8

[43] Delanote I, Wuyts WA, Yserbyt J et al. Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series. BMC pulmonary medicine 2016. DOI: 10.1186/s12890-016-0308-z

[44] Leuschner G, Stocker F, Veit T et al. Outcome of lung transplantation in idiopathic pulmonary fibrosis with previous anti-fibrotic therapy. The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation 2017. DOI: 10.1016/j.healun.2017.07.002

[45] Lambers C, Boehm PM, Lee S et al. Effect of antifibrotics on short-term outcome after bilateral lung transplantation: a multicentre analysis.The European respiratory journal 2018. DOI: 10.1183/13993003.00503-2018

[46] Lancaster L, Crestani B, Hernandez P et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. BMJ open respiratory research 2018. DOI: 10.1136/bmjresp-2018-000397

[47] Guenther A, Krauss E, Tello S, Wagner J et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respiratory research 2018. DOI: 10.1186/s12931-018-0845-5

[48] Behr J, Prasse A, Wirtz H 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. The European respiratory journal 2020. DOI: 10.1183/13993003.02279-2019

[49] Mooney J, Reddy SR, Chang E et al. Antifibrotic therapies reduce mortality and hospitalization among Medicare beneficiaries with idiopathic pulmonary fibrosis. Journal of managed care & specialty pharmacy 2021. DOI: 10.18553/jmcp.2021.27.12.1724

[50] Lasky JA, Criner GJ, Lazarus HM et al. Safety of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis: Global Pharmacovigilance Data. Advances in therapy 2020. DOI: 10.1007/s12325-020-01452-5

[51] Nakazato H, Oku H, Yamane S et al. A novel anti-fibrotic agent pirfenidone suppresses tumor necrosis factor-alpha at the translational level. European journal of pharmacology 2002. DOI: 10.1016/s0014-2999(02)01758-2

[52] Kolb M, Bonella F, Wollin L. Therapeutic targets in idiopathic pulmonary fibrosis. Respiratory medicine 2017. DOI: 10.1016/j.rmed.2017.07.062

[53] Ghazipura M, Mammen MJ, Bissell BD et al. Pirfenidone in Progressive Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2022 Jun;19(6):1030-1039. DOI: 10.1513/AnnalsATS.202103-342OC

[54] Raghu G, Johnson WC, Lockhart D et al. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. American journal of respiratory and critical care medicine 1999. DOI: 10.1164/ajrccm.159.4.9805017

[55] Azuma A, Nukiwa T, Tsuboi E et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis.American journal of respiratory and critical care medicine 2005. DOI: 10.1164/rccm.200404-571OC

[56] Taniguchi H, Ebina M, Kondoh Y et al. Pirfenidone in idiopathic pulmonary fibrosis. The European respiratory journal 2010. DOI: 10.1183/09031936.00005209

[57] Noble PW, Albera C, Bradford WZ et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. The Lancet (London, England) 2011. DOI: 10.1016/S0140-6736(11)60405-4

[58] King TE Jr, Bradford WZ, Castro-Bernardini S et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. The New England journal of medicine 2014. DOI: 10.1056/NEJMoa1402582

[59] Noble PW, Albera C, Bradford WZ et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. The European respiratory journal 2016. DOI: 10.1183/13993003.00026-2015

[60] Nathan SD, Albera C, Bradford WZ et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. The Lancet. Respiratory medicine 2016. DOI: 10.1016/S2213-2600(16)30326-5

[61] Costabel U, Albera C, Lancaster LH et al. An Open-Label Study of the Long-Term Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (RECAP).Respiration; international review of thoracic diseases 2017. DOI: 10.1159/000479976

[62] Lancaster L, Albera C, Bradford WZ et al. Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials. BMJ open respiratory research 2016. DOI: 10.1136/bmjresp-2015-000105

[63] Albera C, Costabel U, Fagan EA et al. Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function.The European respiratory journal 2016. DOI: 10.1183/13993003.01966-2015

[64] Nathan SD, Costabel U, Albera C et al. Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment. Respiratory medicine 2019. DOI: 10.1016/j.rmed.2019.04.016

[65] Ley B, Swigris J, Day BM et al. Pirfenidone Reduces Respiratory-related Hospitalizations in Idiopathic Pulmonary Fibrosis. American journal of respiratory and critical care medicine 2017. DOI: 10.1164/rccm.201701-0091OC

[66] Nathan SD, Costabel U, Glaspole I et al. Efficacy of Pirfenidone in the Context of Multiple Disease Progression Events in Patients With Idiopathic Pulmonary Fibrosis. Chest 2019. DOI: 10.1016/j.chest.2018.11.008

[67] Glassberg MK, Wijsenbeek MS, Gilberg F et al. Effect of pirfenidone on breathlessness in patients with idiopathic pulmonary fibrosis. The European respiratory journal 2019. DOI: 10.1183/13993003.00399-2019

[68] Costabel U, Albera C, Glassberg MK et al. Effect of pirfenidone in patients with more advanced idiopathic pulmonary fibrosis.Respiratory research 2019. DOI: 10.1186/s12931-019-1021-2

[69] Kreuter M, Lederer DJ, Cottin V et al. Concomitant medications and clinical outcomes in idiopathic pulmonary fibrosis. The European respiratory journal 2019. DOI: 10.1183/13993003.01188-2019

[70] Cottin V, Koschel D, Günther A et al. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. ERJ open research 2018. DOI: 10.1183/23120541.00084-2018

[71] Bonella F, Wessendorf TE, Costabel U. Clinical experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis. Deutsche medizinische Wochenschrift (1946) 2013. DOI: 10.1055/s-0032-1332930

[72] Oltmanns U, Kahn N, Palmowski K et al. Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. Respiration; international review of thoracic diseases 2014. DOI: 10.1159/000363064

[73] Loeh B, Drakopanagiotakis F, Bandelli GP et al. Intraindividual response to treatment with pirfenidone in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine 2015. DOI: 10.1164/rccm.201406-1106LE

[74] van Manen MJG, Birring SS, Vancheri C et al. Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis. The European respiratory journal 2017. DOI: 10.1183/13993003.01157-2017

[75] Raghu G, Amatto VC, Behr J, Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. The European respiratory journal 2015. DOI: 10.1183/13993003.02316-2014

[76] Allaix ME, Fisichella PM, Noth I et al. The pulmonary side of reflux disease: from heartburn to lung fibrosis. Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract 2013. DOI: 10.1007/s11605-013-2208-3

[77] Raghu G, Pellegrini CA, Yow E et al. Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial. The Lancet. Respiratory medicine 2018. DOI: 10.1016/S2213-2600(18)30301-1

[78] Tran T, Suissa S. The effect of anti-acid therapy on survival in idiopathic pulmonary fibrosis: a methodological review of observational studies.The European respiratory journal 2018. DOI: 10.1183/13993003.00376-2018

[79] Kreuter M, Spagnolo P, Wuyts W et al. Antacid Therapy and Disease Progression in Patients with Idiopathic Pulmonary Fibrosis Who Received Pirfenidone. Respiration; international review of thoracic diseases 2017. DOI: 10.1159/000468546

[80] Kreuter M, Wuyts W, Renzoni E et al. Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. The Lancet. Respiratory medicine 2016. DOI: 10.1016/S2213-2600(16)00067-9

[81] Tran T, Suissa S. Comparing New-User Cohort Designs: The Example of Proton Pump Inhibitor Effectiveness in Idiopathic Pulmonary Fibrosis. American journal of epidemiology 2021. DOI: 10.1093/aje/kwaa242

[82] Tran T, Assayag D, Ernst P et al. Effectiveness of Proton Pump Inhibitors in Idiopathic Pulmonary Fibrosis: A Population-Based Cohort Study. Chest 2021. DOI: 10.1016/j.chest.2020.08.2080

[83] Demedts M, Behr J, Buhl R, Costabel U et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis.The New England journal of medicine 2005. DOI: 10.1056/NEJMoa042976

[84] Martinez FJ, de Andrade JA, Anstrom KJ et al. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis.The New England journal of medicine 2014. DOI:10.1056/NEJMoa1401739

[85] Feng F, Zhang J, Wang Z et al. Efficacy and safety of N-acetylcysteine therapy for idiopathic pulmonary fibrosis: An updated systematic review and meta-analysis. Experimental and therapeutic medicine 2019. DOI: 10.3892/etm.2019.7579

[86] Behr J, Bendstrup E, Crestani B et al. Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet. Respiratory medicine 2016. DOI: 10.1016/S2213-2600(16)30044-3

[87] Shi H, Yin D, Bonella F et al. Efficacy, safety, and tolerability of combined pirfenidone and N-acetylcysteine therapy: a systematic review and meta-analysis. BMC pulmonary medicine 2020. DOI: 10.1186/s12890-020-1121-2

[88] Sakamoto S, Kataoka K, Kondoh Y et al. Pirfenidone plus inhaled N-acetylcysteine for idiopathic pulmonary fibrosis: a randomised trial. The European respiratory journal 2021. DOI: 10.1183/13993003.00348-2020

[89] Oldham JM, Ma SF, Martinez FJ et al. TOLLIP, MUC5B, and the Response to N-Acetylcysteine among Individuals with Idiopathic Pulmonary Fibrosis. American journal of respiratory and critical care medicine 2015. DOI: 10.1164/rccm.201505-1010OC

[90] Oldham JM, Witt LJ, Adegunsoye A et al. N-acetylcysteine exposure is associated with improved survival in anti-nuclear antibody seropositive patients with usual interstitial pneumonia. BMC pulmonary medicine 2018. DOI: 10.1186/s12890-018-0599-3

[91] Raja SG. Macitentan, a tissue-targeting endothelin receptor antagonist for the potential oral treatment of pulmonary arterial hypertension and idiopathic pulmonary fibrosis. Current opinion in investigational drugs (London, England: 2000) 2010.

[92] King TE Jr. Bosentan for idiopathic pulmonary fibrosis. Current opinion in investigational drugs (London, England: 2000) 2008.

[93] King TE Jr, Behr J, Brown KK et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine 2008. DOI: 10.1164/rccm.200705-732OC

[94] King TE Jr, Brown KK, Raghu G et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. American journal of respiratory and critical care medicine 2001. DOI: 10.1164/rccm.201011-1874OC

[95] Raghu G, Million-Rousseau R, Morganti A et al. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. The European respiratory journal 2013. DOI: 10.1183/09031936.00104612

[96] Corte TJ, Keir GJ, Dimopoulos K et al. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. American journal of respiratory and critical care medicine 2014. DOI: 10.1164/rccm.201403-0446OC

[97] Zisman DA, Schwarz M, Anstrom KJ et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. The New England journal of medicine 2010. DOI: 10.1056/NEJMoa1002110

[98] Jackson RM, Glassberg MK, Ramos CF et al. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. Lung 2010. DOI: 10.1007/s00408-009-9209-8

[99] Han MK, Bach DS, Hagan PG et al. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. Chest 2013. DOI: 10.1378/chest.12-1594

[100] Behr J, Nathan SD, Wuyts WA et al. Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. The Lancet. Respiratory medicine 2021. DOI: 10.1016/S2213-2600(20)30356-8

[101] Behr J, Nathan SD, Harari S et al. Sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: A Phase IIb, randomised, double-blind, placebo-controlled study - Rationale and study design. Respiratory medicine 2018. DOI: 10.1016/j.rmed.2018.03.019

[102] Behr J, Kolb M, Song JW et al. Nintedanib and Sildenafil in Patients with Idiopathic Pulmonary Fibrosis and Right Heart Dysfunction. A Prespecified Subgroup Analysis of a Double-Blind Randomized Clinical Trial (INSTAGE). American journal of respiratory and critical care medicine 2019. DOI: 10.1164/rccm.201903-0488OC

[103] Cottin V, Richeldi L, Rosas I. Nintedanib and immunomodulatory therapies in progressive fibrosing interstitial lung diseases. Respiratory research 2021. DOI: 10.1186/s12931-021-01668-1

[104] Yamagata A, Arita M, Tachibana H et al. Impact of bronchoalveolar lavage lymphocytosis on the effects of anti-inflammatory therapy in idiopathic non-specific interstitial pneumonia, idiopathic pleuroparenchymal fibroelastosis, and unclassifiable idiopathic interstitial pneumonia. Respiratory research 2021. DOI: 10.1186/s12931-021-01726-8

[105] Wijsenbeek M, Kreuter M, Olson A et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management.Current medical research and opinion 2019. DOI: 10.1080/03007995.2019.1647040

[106] Takizawa A, Kamita M, Kondoh Y et al. Current monitoring and treatment of progressive fibrosing interstitial lung disease: a survey of physicians in Japan, the United States, and the European Union. Current medical research and opinion 2021. DOI: 10.1080/03007995.2020.1860920

[107] Teoh AKY, Corte TJ. Nonspecific Interstitial Pneumonia. Seminars in respiratory and critical care medicine 2020. DOI: 10.1055/s-0040-1708499

[108] Lee JY, Jin SM, Lee BJ et al. Treatment response and long term follow-up results of nonspecific interstitial pneumonia. Journal of Korean medical science 2012. DOI: 10.3346/jkms.2012.27.6.661

[109] Nanki N, Fujita J, Yamaji Y et al. Nonspecific interstitial pneumonia/fibrosis completely recovered by adding cyclophosphamide to corticosteroids. Internal medicine (Tokyo, Japan) 2002, DOI: 10.2169/internalmedicine.41.867

[110] Corte TJ, Ellis R, Renzoni EA et al. Use of intravenous cyclophosphamide in known or suspected, advanced non-specific interstitial pneumonia. Sarcoidosis, vasculitis, and diffuse lung diseases: official journal of WASOG 2009.

[111] Kondoh Y, Taniguchi H, Yokoi T et al. Cyclophosphamide and low-dose prednisolone in idiopathic pulmonary fibrosis and fibrosing nonspecific interstitial pneumonia. The European respiratory journal 2005. DOI: 10.1183/09031936.05.00071004

[112] Morisset J, Johannson KA, Vittinghoff E et al. Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis. Chest 2017. DOI: 10.1016/j.chest.2016.10.029

[113] Adegunsoye A, Oldham JM, Fernández Pérez ER et al. Outcomes of immunosuppressive therapy in chronic hypersensitivity pneumonitis. ERJ open research 2017. DOI: 10.1183/23120541.00016-2017

[114] Ferreira M, Borie R, Crestani B et al. Efficacy and safety of rituximab in patients with chronic hypersensitivity pneumonitis (cHP): A retrospective, multicentric, observational study. Respiratory medicine 2020. DOI: 10.1016/j.rmed.2020.106146

[115] Fernández Pérez ER, Swigris JJ, Forssén AV et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. Chest 2013. DOI: 10.1378/chest.12-2685

[116] Raghu G, Remy-Jardin M, Ryerson CJ et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline.American journal of respiratory and critical care medicine 2020. DOI: 10.1164/rccm.202005-2032ST

[117] De Sadeleer LJ, Hermans F, De Dycker E et al. Effects of Corticosteroid Treatment and Antigen Avoidance in a Large Hypersensitivity Pneumonitis Cohort: A Single-Centre Cohort Study. Journal of clinical medicine 2018. DOI: 10.3390/jcm8010014

[118] Juge PA, Solomon JJ, van Moorsel CHM et al. MUC5B promoter variant rs35705950 and rheumatoid arthritis associated interstitial lung disease survival and progression. Seminars in arthritis and rheumatism 2021. DOI: 10.1016/j.semarthrit.2021.07.002

[119] Juge PA, Lee JS, Ebstein E et al. MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease. The New England journal of medicine 2018. DOI: 10.1056/NEJMoa1801562

[120] Kiely P, Busby AD, Nikiphorou E et al. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. BMJ open 2019. DOI: 10.1136/bmjopen-2018-028466

[121] Conway R, Low C, Coughlan RJ et al. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. BMJ (Clinical research ed.) 2015. DOI: 10.1136/bmj.h1269

[122] Huang S, Kronzer VL, Dellaripa PF et al. Rheumatoid arthritis-associated interstitial lung disease: Current update on prevalence, risk factors, and pharmacologic treatment.Current treatment options in rheumatology 2020. DOI: 10.1007/s40674-020-00160-z

[123] Seeliger B, Prasse A. Immunomodulation in Autoimmune Interstitial Lung Disease.Respiration; international review of thoracic diseases 2020. DOI: 10.1159/000511200

[124] Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review.Seminars in arthritis and rheumatism 2014. DOI: 10.1016/j.semarthrit.2013.09.005

[125] Druce KL, Iqbal K, Watson KD et al. Mortality in patients with interstitial lung disease treated with rituximab or TNFi as a first biologic. RMD open 2017. DOI: 10.1136/rmdopen-2017-000473

[126] Lee CT, Strek ME. The other connective tissue disease-associated interstitial lung diseases: Sjogren's syndrome, mixed connective tissue disease, and systemic lupus erythematosus. Current opinion in pulmonary medicine 2021. DOI: 10.1097/MCP.0000000000000791

[127] Parambil JG, Myers JL, Lindell RM et al. Interstitial lung disease in primary Sjögren syndrome. Chest 2006. DOI: 10.1378/chest.130.5.1489

[128] Fujisawa T, Hozumi H, Kono M et al. Prognostic factors for myositis-associated interstitial lung disease. PloS one 2014. DOI: 10.1371/journal.pone.0098824

[129] Wu W, Guo L, Fu Y et al. Interstitial Lung Disease in Anti-MDA5 Positive Dermatomyositis. Clinical reviews in allergy & immunology 2021. DOI: 10.1007/s12016-020-08822-5

[130] Yamasaki Y, Yamada H, Yamasaki M et al. Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology (Oxford, England) 2007. DOI: 10.1093/rheumatology/kel112

[131] Huapaya JA, Silhan L, Pinal-Fernandez I et al. Long-Term Treatment With Azathioprine and Mycophenolate Mofetil for Myositis-Related Interstitial Lung Disease. Chest 2019. DOI: 10.1016/j.chest.2019.05.023

[132] Takada K, Katada Y, Ito S et al. Impact of adding tacrolimus to initial treatment of interstitial pneumonitis in polymyositis/dermatomyositis: a single-arm clinical trial.Rheumatology (Oxford, England) 2020. DOI: 10.1093/rheumatology/kez394

[133] Fujisawa T, Hozumi H, Kamiya Y et al. Prednisolone and tacrolimus versus prednisolone and cyclosporin A to treat polymyositis/dermatomyositis-associated ILD: A randomized, open-label trial. Respirology (Carlton, Vic.) 2021. DOI: 10.1111/resp.13978

[134] Tsuji H, Nakashima R, Hosono Y et al. Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy With High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis. Arthritis rheumatology (Hoboken, N.J.) 2020. DOI: 10.1002/art.41105

[135] Chen Z, Wang X, Ye S. Tofacitinib in Amyopathic Dermatomyositis-Associated Interstitial Lung Disease. The New England journal of medicine 2019. DOI: 10.1056/NEJMc1900045

[136] He C, Li W, Xie Q et al. Rituximab in the Treatment of Interstitial Lung Diseases Related to Anti-Melanoma Differentiation-Associated Gene 5 Dermatomyositis: A Systematic Review. Frontiers in immunology 2021. DOI: 10.3389/fimmu.2021.820163

[137] Allenbach Y, Guiguet M, Rigolet A et al. Efficacy of Rituximab in Refractory Inflammatory Myopathies Associated with Anti- Synthetase Auto-Antibodies: An Open-Label, Phase II Trial. PloS one 2015. DOI: 10.1371/journal.pone.0133702

[138] Ebata S, Yoshizaki A, Fukasawa T et al. Percentage of residual B cells after 2 weeks of rituximab treatment predicts the improvement of systemic sclerosis-associated interstitial lung disease. J Dermatol. 2022. DOI: 10.1111/1346-8138.16206.

[139] Tashkin DP, Elashoff R, Clements PJ et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med. 2007 Nov 15;176(10):1026-34. DOI: 10.1164/rccm.200702-326OC

[140] Hoyles RK, Ellis RW, Wellsbury J et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis and rheumatism 2006. DOI: 10.1002/art.22204

[141] Tashkin DP, Elashoff R, Clements PJ et al. Cyclophosphamide versus placebo in scleroderma lung disease. The New England journal of medicine 2006. DOI: 10.1056/NEJMoa055120

[142] Tashkin DP, Roth MD, Clements PJ et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. The Lancet. Respiratory medicine 2016. DOI: 10.1016/S2213-2600(16)30152-7

[143] Highland KB, Distler O, Kuwana M et al. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. The Lancet. Respiratory medicine 2021. DOI: 10.1016/S2213-2600(20)30330-1

[144] Khanna D, Denton CP, Lin CJF et al. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). Annals of the rheumatic diseases 2018. DOI: 10.1136/annrheumdis-2017-211682

[145] Khanna D, Lin CJF, Furst DE et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. Respiratory medicine 2020. DOI: 10.1016/S2213-2600(20)30318-0

[146] Satoshi Ebata, MD; Ayumi Yoshizaki, MD; Koji Oba et al. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. The Lancet Rheumatology 2021. DOI: 10.1016/S2665-9913(22)00131-X

[147] Sircar G, Goswami RP, Sircar D et al. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. Rheumatology (Oxford, England) 2018. DOI: 10.1093/rheumatology/key213

[148] Burt RK, Shah SJ, Dill K et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet (London, England) 2011. DOI: 10.1016/S0140-6736(11)60982-3

[149] van Laar JM, Nihtyanova SI, Naraghi K et al. Autologous HSCT for systemic sclerosis. Lancet (London, England) 2013. DOI: 10.1016/S0140-6736(13)61239-8

[150] Sullivan KM, Goldmuntz EA, Keyes-Elstein L et al. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. The New England journal of medicine 2018. DOI: 10.1056/nejmoa1703327

[151] Henes J, Oliveira MC, Labopin M et al. Autologous stem cell transplantation for progressive systemic sclerosis: a prospective non-interventional study from the European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party. Haematologica 2021. DOI: 10.3324/haematol.2019.230128

[152] Finnerty JP, Ponnuswamy A, Dutta P et al. Efficacy of antifibrotic drugs, nintedanib and pirfenidone, in treatment of progressive pulmonary fibrosis in both idiopathic pulmonary fibrosis (IPF) and non-IPF: a systematic review and meta-analysis. BMC pulmonary medicine 2021. DOI: 10.1186/s12890-021-01783-1

[153] Nasser M, Si-Mohamed S, Turquier S et al. Nintedanib in idiopathic and secondary pleuroparenchymal fibroelastosis. Orphanet journal of rare diseases 2021. DOI: 10.1186/s13023-021-02043-5

[154] Inoue Y, Suda T, Kitamura H et al. 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. Respiratory medicine 2021. DOI: 10.1016/j.rmed.2021.106574

[155] Flaherty KR, Wells AU, Cottin V et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. The European respiratory journal 2022. DOI: 10.1183/13993003.04538-2020

[156] Maher TM, Brown KK, Kreuter M et al. Effects of nintedanib by inclusion criteria for progression of interstitial lung disease. The European respiratory journal 2022. DOI: 10.1183/13993003.04587-2020

[157] Behr J, Günther A, Bonella F et al. German Guideline for Idiopathic Pulmonary Fibrosis - Update on Pharmacological Therapies 2017. Pneumologie (Stuttgart, Germany) 2018. DOI: 10.1055/s-0043-123035

[158] Wells AU, Flaherty KR, Brown KK 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. The Lancet. Respiratory medicine 2020. DOI: 10.1016/S2213-2600(20)30036-9

[159] Solomon JJ, Danoff SK, Goldberg HJ et al. The Design and Rationale of the Trail1 Trial: A Randomized Double-Blind Phase 2 Clinical Trial of Pirfenidone in Rheumatoid Arthritis-Associated Interstitial Lung Disease. Advances in therapy 2019. DOI: 10.1007/s12325-019-01086-2

[160] Lettieri CJ, Nathan SD, Barnett SD et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006. DOI: 10.1378/chest.129.3.746

[161] King TE Jr, Tooze JA, Schwarz MI et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. American journal of respiratory and critical care medicine 2001. DOI: 10.1164/ajrccm.164.7.2003140

[162] Olschewski H, Ghofrani HA, Walmrath D et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. American journal of respiratory and critical care medicine 1999. DOI: 10.1164/ajrccm.160.2.9810008

[163] Waxman A, Restrepo-Jaramillo R, Thenappan T et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. The New England journal of medicine 2021. DOI: 10.1056/NEJMoa2008470

[164] Swigris JJ, Wamboldt FS, Behr J et al. The 6 minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference. Thorax 2010. DOI: 10.1136/thx.2009.113498

[165] Rose F, Zwick K, Ghofrani HA et al. Prostacyclin enhances stretch-induced surfactant secretion in alveolar epithelial type II cells. American journal of respiratory and critical care medicine 1999. DOI: 10.1164/ajrccm.160.3.9812155

[166] Bauman KA, Wettlaufer SH, Okunishi K et al. The antifibrotic effects of plasminogen activation occur via prostaglandin E2 synthesis in humans and mice. The Journal of clinical investigation 2010. DOI: 10.1172/JCI38369

[167] Lama V, Moore BB, Christensen P et al. Prostaglandin E2 synthesis and suppression of fibroblast proliferation by alveolar epithelial cells is cyclooxygenase-2-dependent. American journal of respiratory cell and molecular biology 2002. DOI: 10.1165/rcmb.4857

[168] Maher TM, Stowasser S, Nishioka Y et al. Biomarkers of extracellular matrix turnover in patients with idiopathic pulmonary fibrosis given nintedanib (INMARK study): a randomised, placebo-controlled study. The Lancet. Respiratory medicine 2019. DOI: 10.1016/S2213-2600(19)30255-3

[169] Taguchi Y, Ebina M, Hashimoto S et al. Efficacy of pirfenidone and disease severity of idiopathic pulmonary fibrosis: Extended analysis of phase III trial in Japan. Respiratory investigation 2015. DOI: 10.1016/j.resinv.2015.06.002

[170] Wells AU, Brown KK, Cottin V. The progressive fibrotic phenotype in current clinical practice. Current opinion in pulmonary medicine 2021. DOI: 10.1097/MCP.0000000000000805

[171] Adegunsoye A, Oldham JM, Bellam SK et al. Computed Tomography Honeycombing Identifies a Progressive Fibrotic Phenotype with Increased Mortality across Diverse Interstitial Lung Diseases. Annals of the American Thoracic Society 2019. DOI: 10.1513/AnnalsATS.201807-443OC

[172] Salisbury ML, Gu T, Murray S et al. Hypersensitivity Pneumonitis: Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory. Chest 2019. DOI: 10.1016/j.chest.2018.08.1076

[173] Richeldi L, Kreuter M, Selman M et al. Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. Thorax 2018. DOI: 10.1136/thoraxjnl-2016-209701

[174] Suzuki Y, Mori K, Aono Y et al. Switching antifibrotics in patients with idiopathic pulmonary fibrosis: a multi-center retrospective cohort study. BMC pulmonary medicine 2021. DOI: 10.1186/s12890-021-01587-3

[175] Vianello A, Salton F, Molena B et al. Nintedanib Treatment for Idiopathic Pulmonary Fibrosis Patients Who Have Been Switched from Pirfenidone Therapy: A Retrospective Case Series Study. Journal of clinical medicine 2020. DOI: 10.3390/jcm9020422

[176] Milger K, Kneidinger N, Neurohr C et al. Switching to nintedanib after discontinuation of pirfenidone due to adverse events in IPF. The European respiratory journal 2015. DOI: 10.1183/13993003.00584-2015

[177] Adams CJ, Shapera S, Ryerson CJ et al. Effect of continued antifibrotic therapy after forced vital capacity decline in patients with idiopathic pulmonary fibrosis; a real world multicenter cohort study. Respiratory medicine 2022. DOI: 10.1016/j.rmed.2021.106722

[178] Nathan SD, Albera C, Bradford WZ et al. Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax 2016. DOI: 10.1136/thoraxjnl-2015-207011

[179] Richeldi L, Crestani B, Azuma A et al. Outcomes following decline in forced vital capacity in patients with idiopathic pulmonary fibrosis: Results from the INPULSIS and INPULSIS-ON trials of nintedanib. Respiratory medicine 2019. DOI: 10.1016/j.rmed.2019.08.002

[180] Behr J, Günther A, Kreuter M et al. Expert Knowledge and Supporting Advice for the Clinical Use of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis. Pneumologie (Stuttgart, Germany) 2017. DOI: 10.1055/s-0043-109856

[181] Lancaster LH, de Andrade JA, Zibrak JD et al. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. European respiratory review : an official journal of the European Respiratory Society 2017. DOI: 10.1183/16000617.0057-2017

[182] Costabel U, Bendstrup E, Cottin V et al. Pirfenidone in idiopathic pulmonary fibrosis: expert panel discussion on the management of drug-related adverse events. Advances in therapy 2014. DOI: 10.1007/s12325-014-0112-1

[183] Wuyts WA, Antoniou KM, Borensztajn K et al. Combination therapy: the future of management for idiopathic pulmonary fibrosis? The Lancet. Respiratory medicine 2014. DOI: 10.1016/S2213-2600(14)70232-2

[184] Ogura T, Taniguchi H, Azuma A et al. Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis. The European respiratory journal 2015. DOI: 10.1183/09031936.00198013

[185] Vancheri C, Kreuter M, Richeldi L et al. Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis. Results of the INJOURNEY Trial. American journal of respiratory and critical care medicine 2018. DOI: 10.1164/rccm.201706-1301OC

[186] Flaherty KR, Fell CD, Huggins JT et al. Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis. The European respiratory journal 2018. DOI: 10.1183/13993003.00230-2018

[187] Hisata S, Bando M, Homma S et al. Safety and tolerability of combination therapy with pirfenidone and nintedanib for idiopathic pulmonary fibrosis: A multicenter retrospective observational study in Japan. Respiratory investigation 2021. DOI: 10.1016/j.resinv.2021.04.005

[188] du Bois RM, Weycker D, Albera C et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. American journal of respiratory and critical care medicine 2011. DOI: 10.1164/rccm.201105-0840OC

[189] Chung MP, Park MS, Oh IJ et al. Safety and Efficacy of Pirfenidone in Advanced Idiopathic Pulmonary Fibrosis: A Nationwide Post-Marketing Surveillance Study in Korean Patients. Advances in therapy 2020. DOI: 10.1007/s12325-020-01328-8

[190] Yoon HY, Kim DS, Song JW. Efficacy and Safety of Pirfenidone in Advanced Idiopathic Pulmonary Fibrosis.Respiration; international review of thoracic diseases 2019. DOI: 10.1159/000492937

[191] Raghu G, Anstrom KJ, King TE Jr et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. The New England journal of medicine 2012. DOI: 10.1056/NEJMoa1113354

[192] Park Y, Ahn C, Kim TH. Occupational and environmental risk factors of idiopathic pulmonary fibrosis: a systematic review and meta-analyses. Sci Rep. 2021 Mar 2;11(1):4318. doi: 10.1038/s41598-021-81591-z

[193] Abramson MJ, Murambadoro T, Alif SM et al. Australian IPF Registry. Occupational and environmental risk factors
for idiopathic pulmonary fibrosis in Australia: case-control study. Thorax. 2020 Oct;75(10):864-869. doi: 10.1136/thoraxjnl-2019-214478.

[194] Miedema JR, Moor CC, Veltkamp M et al. Safety and tolerability of pirfenidone in asbestosis: a prospective multicenter study. Respir Res. 2022 May 28;23(1):139. doi: 10.1186/s12931-022-02061-2

[195] Bonella F, Cottin V, Valenzuela C et al. Meta-Analysis of Effect of Nintedanib on Reducing FVC Decline Across Interstitial Lung Diseases. Adv Ther. 2022 Jul;39(7):3392-3402. doi: 10.1007/s12325-022-02145-x

[196] Zeng Y, Jiang Y, Banks DE. The Effectiveness of Whole Lung Lavage in Pneumoconiosis: A Systematic Review and Meta-Analysis. J Occup Environ Med. 2022 Aug 1;64(8):e492-e499. doi: 10.1097/JOM.0000000000002599

[197] Newton CA, Zhang D, Oldham JM etal. Telomere Length and Use of Immunosuppressive Medications in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2019 Aug 1;200(3):336-347. doi: 10.1164/rccm.201809-1646OC

[198] Humbert, M.; Kovacs, G.; Hoeper, M.M.; Badagliacca, R.; Berger, R.M.; Brida, M.; Carlsen, J.; Coats, A.J.; Escribano-Subias, P.; Ferrari, P.; et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur. Respir. J. 2023, 61, 2200879.

[199] Behr J, Nathan SD, Costabel U, Albera C, Wuyts WA, Glassberg MK, Haller H Jr, Alvaro G, Gilberg F, Samara K, Lancaster L. Efficacy and Safety of Pirfenidone in Advanced Versus Non-Advanced Idiopathic Pulmonary Fibrosis: Post-Hoc Analysis of Six Clinical Studies. Adv Ther. 2023 Sep;40(9):3937-3955. doi: 10.1007/s12325-023-02565-3. Epub 2023 Jun 30. PMID: 37391667; PMCID: PMC10427557.

Figure legends:

Figure 1: Overview of interstitial lung diseases (ILDs) which may manifest as progressive pulmonary fibrosis (PPF). The areas marked orange in each box are the estimated share of patients with progressive fibrotic manifestations in the respective diagnostic groups. The diagram does not cover idiopathic pulmonary fibrosis (IPF).

* The committee acknowledges that eosinophilic pneumonia of unknown cause was not included in the IIP classification.

** Myositis includes polymyositis/dermatomyositis/antisynthetase syndrome, which may also be amyopathic.

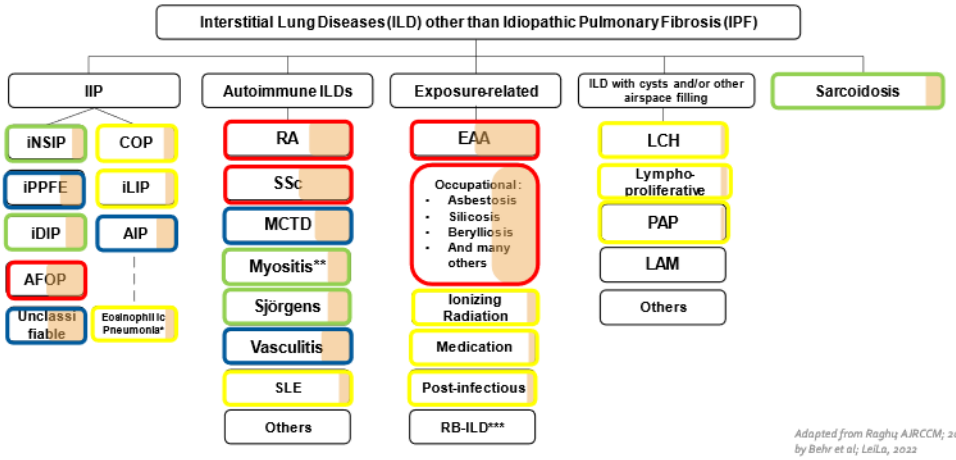
*** Although respiratory bronchiolitis interstitial lung disease (RBILD) is acknowledged to be a consequence of cigarette smoke in virtually all patients with

RBILD, RBILD and desquamative interstitial pneumonia (DIP) often coexist.

DIP is rarely seen in patients without exposure to cigarette smoke.

Abbreviations

AFOP = acute fibrinous and organizing pneumonia;
AIP = acute interstitial pneumonia;
COP = cryptogenic organizing pneumonia;
DM = dermatomyositis;
HP = hypersensitivity pneumonitis (extrinsic allergic alveolitis);
iDIP = idiopathic desquamative interstitial pneumonia;
IIP = idiopathic interstitial pneumonia;
iLIP = idiopathic lymphoid interstitial pneumonia;
iNSIP = idiopathic non-specific interstitial pneumonia;
iPPFE = idiopathic pleuroparenchymal fibroelastosis;
LAM = lymphangioleiomyomatosis;
LCH = Langerhans cell histiocytosis;
MCTD = mixed connective tissue disease;
PAP = pulmonary alveolar proteinosis;
PM = polymyositis;
RA = rheumatoid arthritis;
SLE = systemic lupus erythematosus;
SSc = systemic sclerosis.



Adapted from Raghu AJRCCM; 2022 by Behr et al; Lei.La, 2022