Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2026-B-130-z Nerandomilast

Stand: August 2026

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Nerandomilast

Zur Behandlung der progredienten pulmonalen Fibrose (PPF)

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht "II. Zugelassene Arzneimittel im Anwendungsgebiet"*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Lungentransplantation <u>Maßnahmen gemäß Heilmittel-Richtlinie bzw. Heilmittelkatalog:</u> • Physiotherapie/Atemtherapie <u>Maßnahmen gemäß Hilfsmittel-Richtlinie:</u> • Langzeit-Sauerstofftherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• *Nintedanib (Beschluss vom 04. Februar 2020, PF-ILD)* • *[Nintedanib (Beschluss vom 04. Februar 2020, SSc-ILD)* • *Nintedanib (Beschluss vom 17. Oktober 2019, IPF))* • *Pirfenidon (Beschluss vom 15. März 2012, IPF)]*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
BI 1015550	<u>Anwendungsgebiet laut Positive Opinion:</u> Treatment of adult patients with Progressive Pulmonary Fibrosis (PPF). *[inoffizielle Übersetzung: Behandlung von Erwachsenen mit progredienter pulmonaler Fibrose (PPF).]*
Methylprednisolon H02AB04 Methylprednisolon Jenapharm®	<u>Bronchial- und Lungenkrankheiten</u> […] – Interstitielle Lungenerkrankungen, wie akute Alveolitis, Lungenfibrose, zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (Stand FI: April 2018)
Prednisolon H02AB06 generisch	Pneumonologie: […] – interstitielle Lungenerkrankungen wie akute Alveolitis (DS: b), Lungenfibrose (DS: b), Bronchiolitis obliterans organisierende Pneumonie (BOOP) (DS: b ausschleichend), ggf. in Kombination mit Immunsuppressiva, chronische eosinophile Pneumonie (DS: b ausschleichend), zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (DS: b) […] (Stand FI: September 2017)
Prednison H02AB07 generisch	Pneumonologie: […] – interstitielle Lungenerkrankungen wie akute Alveolitis (DS: b), Lungenfibrose (DS: b), Bronchiolitis obliterans organisierende Pneumonie (BOOP) (DS: b ausschleichend), ggf. in Kombination mit Immunsuppressiva, chronische eosinophile Pneumonie (DS: b ausschleichend), zur Langzeittherapie chronischer Formen der Sarkoidose in den Stadien II und III (bei Atemnot, Husten und Verschlechterung der Lungenfunktionswerte) (DS: b) […]

	(Stand FI: September 2017)
Antifibrotische Therapien	
Pirfenidon L04AX05 Esbriet®	Esbriet wird angewendet bei Erwachsenen zur Behandlung von leichter bis mittelschwerer idiopathischer pulmonaler Fibrose (IPF). (Stand FI: April 2018)
Nintedanib L01XE31 Ofev®	Ofev wird angewendet bei Erwachsenen zur Behandlung der idiopathischen Lungenfibrose (IPF). Ofev wird außerdem angewendet bei Erwachsenen zur Behandlung anderer chronischer progredient fibrosierender interstitieller Lungenerkrankungen (ILDs) (siehe Abschnitt 5.1). Ofev wird angewendet zur Behandlung einer interstitiellen Lungenerkrankung bei Erwachsenen mit systemischer Sklerose (SSc-ILD).

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2026-B-130z (Beratung nach § 35a SGB V) Nerandomilast

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. Juni 2026

Inhaltsverzeichnis

Abkürzungsverzeichnis

6MWD	6-Minute Walking Distance
6MWT	6-Minute Walking Test
AE	Adverse event
ATS	American Thoracic Society
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CTD	Connective tissue disease
EMA	European Medicines Agency
ERS	European Respiratory Society
FEV	Forciertes exspiratorisches Volumen
FVC	Forced vital capacity
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
HRQoL	Health-related quality of life
iNSIP	Idiopathic non-specific interstitial pneumonia
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
JRS	Japanese Respiratory Society
KI	Konfidenzintervall
LIP	Lymphoid interstitial pneumonia
LoE	Level of Evidence
MA-ILD	Myositis-assoziierte ILD
NICE	National Institute for Health and Care Excellence
NSIP	Non-specific interstitial pneumonia
OR	Odds Ratio
PF-ILD	Progressive fibrosing interstitial lung disease
PFT	Pulmonary function test
PH	Pulmonale Hypertonie

PPF	Progrediente Pulmonale Fibrose
PTChP	Polish Respiratory Society
RA-ILD	Rheumatoide Arthritis-assoziierte ILD
RR	Relatives Risiko
SGRQ	St. George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SSc-ILD	Systemische Sklerose-assoziierte ILD
TLC	Total lung capacity
uILD	Unclassifiable interstitial lung disease
UIP	Usual interstitial pneumonia
WHO	World Health Organization

1 Indikation

Behandlung von Erwachsenen mit progredienter pulmonaler Fibrose (PPF).

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *progrediente pulmonale Fibrose* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: *The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed*. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 16.06.2026 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 1564 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Alle eingeschlossenen Referenzen wurden im Volltext beschafft. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen im Volltext gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Chong W et al., 2024 [1].

A systematic review and meta-analysis of the clinical benefits and adverse reactions of anti-fibrotics in non-IPF progressive fibrosing ILD

Fragestellung

Anti-fibrotics can reduce restrictive impairment in idiopathic pulmonary fibrosis (IPF). However, its effectiveness in non-IPF progressive fibrosing interstitial lung disease (non-IPF PF-ILD) remains uncertain. Objective: We assess the efficacy and safety of anti-fibrotics pirfenidone and nintedanib versus placebo among non-IPF PF-ILD adult patients

Methodik

Population:

- non-IPF PF-ILD adult patients
  - Non-IPF PF-ILD was either classifiable as connective tissue disease-associated interstitial lung disease (CTD-ILD), fibrotic hypersensitivity pneumonitis (HP), idiopathic non-specific interstitial pneumonia (NSIP), sarcoidosis, interstitial pneumonia with autoimmune features (IPAF), drug/environmental-related ILD, or unclassifiable.

Intervention:

- anti-fibrotic therapy) of pirfenidone and nintedanib

Komparator:

- placebo

Endpunkte:

- Primary outcomes assessed were the rate of restrictive impairment observed on PFTs determined by the rate of decline in FVC in milliliters (ml) and the percent (%) predicted.
- Secondary outcomes were the rate of decline in FVC by more than 10 % predicted, functional status based on the decrease in 6MWD in meters, all-cause mortality, and adverse reactions.
  - Adverse reactions or events assessed were nausea/vomiting, diarrhea, and anorexia/weight loss; skin disorders defined as rash, pruritus, and photosensitivity; respiratory disorders defined as cough and dyspnea, upper and lower respiratory tract infection; neurological disorders defined as headache, dizziness, fatigue, and insomnia

Recherche/Suchzeitraum:

- literature search was performed through PubMed, SCOPUS, and Cochrane Central Register of Controlled Trials databases from January 1st, 2000 to December 30th, 2023

Qualitätsbewertung der Studien:

- Six researchers performed quality and risk of bias for each RCTs using the Cochrane Collaboration's Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- seven RCTs were included (1816 patients)

Charakteristika der Population/Studien:

Table 1
Randomized controlled trials characteristics.

RCTs, Year Pirfenidone	Duration [Country]	Intervention N [Control N]	Pirfenidone Dose	Inclusion	Primary Outcome	Secondary Outcome
Acharya et al., 2020[11]	July 2017-December 2018 [India]	17 [17]	200 mg 3x/day, increased by 600 mg/day every week to 2400 mg/day	1) Systemic sclerosis-associated ILD; 2) FVC between 50 and 80 % predicted and DLCO > 30 % predicted; 3) Disease duration < 7 years; 4) No new immunosuppressants within the 6 months; 5) No co-existing inflammatory myopathy, pulmonary hypertension requiring therapy, persistent cytopenia, exposure to biologics, and severely abnormal liver function.	Stabilization or improvement (increase > 10 %) of FVC at 24 weeks	1) Decline in FVC%; 2) Decline in 6MWD.
Behr et al., 2021[12] (RELIEF)	April 2016-October 2018 [Germany]	64 [63]	267 mg 3x/ day for 1st week, 534 mg 3x/day for 2nd week, and 801 mg 3x/day after.	1) Aged 18–80 years with CTD-ILD, fibrotic NSIP, chronic HP, and asbestos-induced lung fibrosis; 2) FVC 40–90 % predicted and DLCO 10–90 % predicted; 3) Either lung biopsies or HRCT done within 6 months 4) Progression with yearly decline in FVC > 5 % predicted within 24 months.	Change in FVC% at 48 weeks	1) Progression-free survival; 2) Decline in FVC of less than 5 %, 5 % to less than 10 %, and at least 10 % predicted; 3) Decline in DLCO ml/min/mm Hg; 4) Decline in 6MWD; 5) SGRQ score; 6) Time to clinical deterioration; 7) Adverse events.
Fernandez Perez et al., 2023[19]	June 2017 - April 2020 [USA]	27 [13]	2403 mg oral daily in divided doses	1) Aged 18–80 years with fibrotic HP; 2) FVC > 40 % predicted and DLCO > 30 % predicted; 3) Visual assessment > 5 % lung involvement on HRCT within 4 months; 4) Progressive disease: worsening respiratory symptoms, worsening fibrosis on HRCT, or decline in FVC > 5 % [redicted within 24 months.	Change in FVC% at 52 weeks	1) Decline in FVC% or DLCO%; 2) Acute respiratory exacerbations; 3) Decline of > 50 m in 6MWD; 4) Increase use of prednisone > 10 mg or initiation of corticosteroids and/or steroid-sparing immunosuppressive agents; 5) Death or adverse events.
Maher et al., 2020[14]	May 2017-June 2018 [78.5 % Europe and remainder in Australia and UK]	127 [126]	2403 mg oral daily	1) Aged 18–85 years with fibrosing unclassifiable ILD; 2) FVC > 45 % predicted and DLCO > 30 % predicted; 3) > 10 % fibrosis on HRCT within 12 months; 4) FEV1/FVC ratio > 70 %; 5) 6MWD > 150 m; 6) Progressive disease: decline in FVC > 5 % predicted or worsening respiratory symptoms after excluding other etiologies within 6 months.	Change in FVC% at 24 weeks	1) FVC Decline >5 % or > 10 % predicted; 2) Decline in DLCO%; 3) Decline in 6MWD; 4) All-cause and respiratory hospital admission; 5) Death or adverse events.
Solomon et al., 2022[15] (TRAIL 1)	May 2017-March 2020 [Australia, Canada, UK and USA]	63 [60]	Three 267 mg tablets 3x/day	1) Aged 18–85 years diagnosed with rheumatoid arthritis associated ILD; 2) FVC > 40 % predicted and DLCO >30 % predicted; 3) >10 % fibrosis on HRCT.	Change in FVC > 10 % or death at 52 weeks	1) Decline in FVC% and ml; 2) Decline in FVC >10 %; 3) Death or adverse events; 4) Health outcomes (hospitalizations, mortality, and exacerbations);

RCTs, Year Nintedanib	Duration [Country]	Intervention N [Control N]	Nintedanib Dose	Inclusion	Primary Outcome	Secondary Outcome
Distler et al., 2019[17] (SENSCIS)	November 2015-October 2017 [32 countries, 60 % Europe, 16 % Asia, 13 % South America and the remainder North America, Australia]	288 [288]	150 mg 2x/ day	1) Aged > 18 with systemic sclerosis-associated ILD; 2) FVC > 40 % predicted and DLCO > 30 % predicted; 3) First non-Raynaud's symptom within 7 years; 4) Receiving prednisolone up to 10 mg per day or stable doses of mycophenolate or methotrexate for at least 6 months	Change in FVC ml at 52 weeks	1) Decline in FVC% and ml; 2) Decline in DLCO%; 3) Decline in FVC > 5 % and > 10 % predicted; 4) Death and adverse events. 5) Change in symptoms severity score of SGRQ and FACIT;
Flaherty et al., 2019[18] (INBUILD)	February 2017-April 2018 [15 countries; 61 % Europe, 13 % North America, 13 %. South America, 13 % Asia]	332 [331]	150 mg 2x/ day	1) Aged > 18 years with progressive fibrosing ILD; 2) FVC > 45 % and DLCO > 30 %; 3) ILD progression within the 24 months with > 10 % predicted FVC decline a relative decline, worsening respiratory symptoms with FVC decline 5–10 % predicted or	Change in FVC % at 52 weeks	1) Acute exacerbation of ILD; 2) Death; 3) Symptomatic Severity Score of K-BILD

(continued on next page)

Table 1 (*continued*)

RCTs, Year Nintedanib	Duration [Country]	Intervention N [Control N]	Nintedanib Dose	Inclusion	Primary Outcome	Secondary Outcome
				increased fibrosis on HRCT, or worsening respiratory symptoms and increased extent of fibrosis.		

Abbreviations: CTD-ILD, connective tissue disease-associated interstitial lung disease; DLCO, diffusion capacity of carbon monoxide; FACIT, Functional Assessment of Chronic Illness Therapy; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; ml, milliliters; mg, milligram; K-BILD, King's Brief Interstitial Lung Disease; N/A, non-available; NSIP, non-specific interstitial pneumonia; RCTs, randomized controlled trials; SGRQ, St. George's Respiratory questionnaire; UK, United Kingdom; USA, United States of America; 6MWD, 6-minute walk distance.

Qualität der Studien:

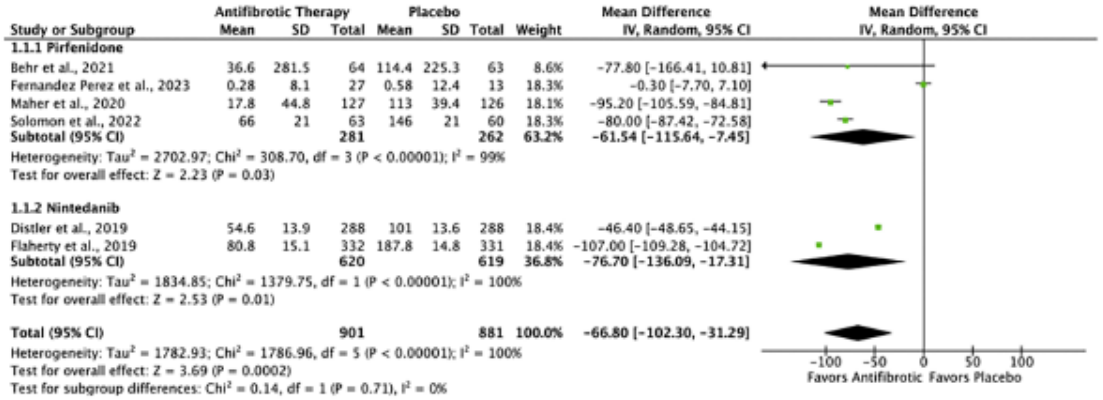
Table 3: The table shows the results of the Cochrane Collaboration's Risk of Bias Tool for the eight randomized controlled trials.

Randomized Controlled Trials	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Acharya et al., 2020[11]	+	+	+	+	+	+	?
Behr et al., 2021[12]	+	+	+	+	+	+	+
Fernandez Perez et al., 2023[19]	+	+	+	+	+	+	+
Maher et al., 2020[14]	+	+	+	+	+	+	+
Solomon et al., 2022[15]	+	+	+	+	+	+	?
Distler et al., 2019[17]	+	+	+	+	+	+	+
Flaherty et al., 2019[18]	+	+	+	+	+	+	+

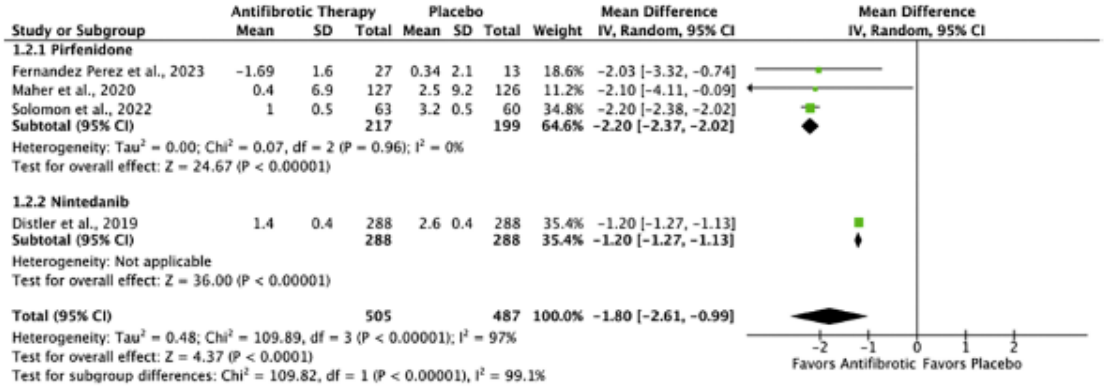
Abbreviations: +, risk of bias low; -, risk of bias high; ?, unknown risk of bias

Studienergebnisse:

A. FVC Decline in ml



B. FVC Decline in %



C. Decrease in 6MWD, Meters

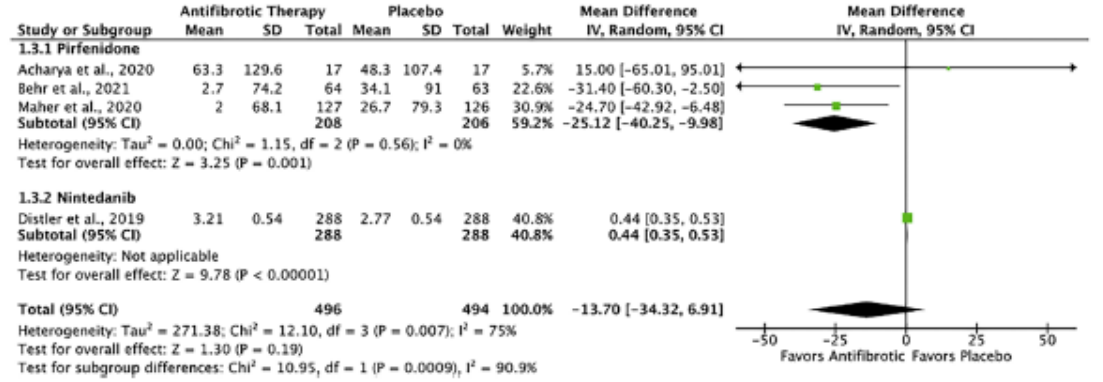
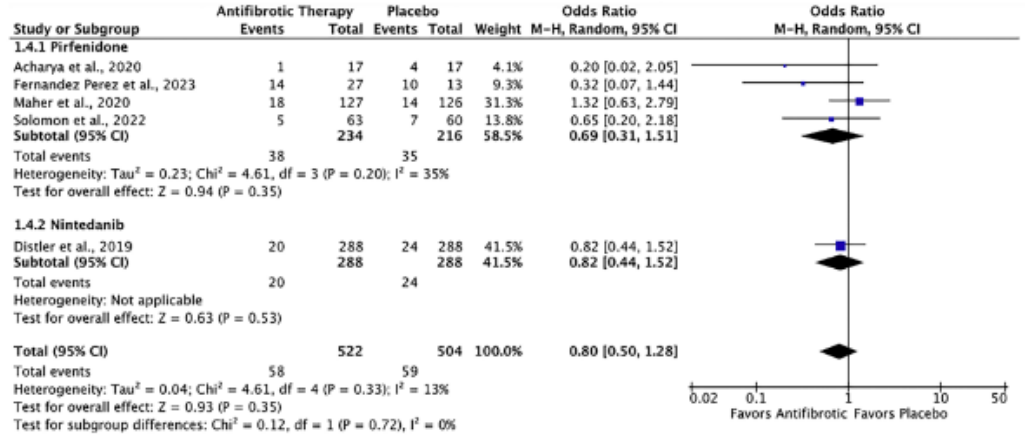


Fig. 2. Forrest plot of non-IPF PF-ILD patients divided into anti-fibrotic versus placebo groups. Outcomes of FVC decline in milliliters (Fig. 2A), percent predicted (Fig. 2B), and six-minute walk distance (Fig. 2C) were assessed. Sensitivity analysis was also performed for patients receiving either anti-fibrotic of pirfenidone or nintedanib. Mean differences were calculated by the inverse variance statistical method with a random-effects model.].

Abbreviations: CI: confidence interval; FVC: forced vital capacity; IV: inverse variance; ml: milliliters; SD: standard deviation;%; percent predicted, 6MWD: six-minute walk distance.

A. FVC Decline > 10% Predicted



B. All-Cause Mortality

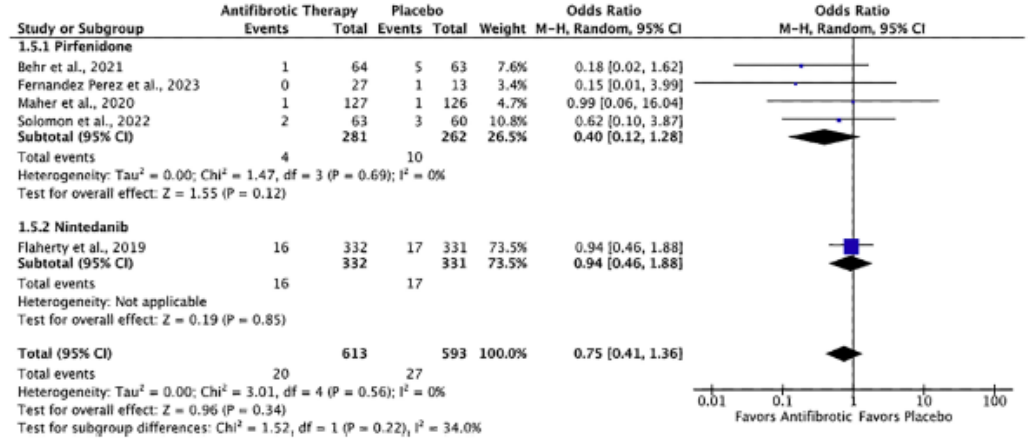


Fig. 3. Forrest plot of non-IPF PF-ILD patients divided into anti-fibrotic versus placebo groups. The outcomes of FVC decline by more than 10 % predicted (Fig. 3A) and all-cause mortality (Fig. 3B). The odds ratio was calculated by the Mantel-Haenszel method with a random-effects model.
Abbreviations: CI, confidence interval; FVC: forced vital capacity; MH, Mantel-Haenszel.

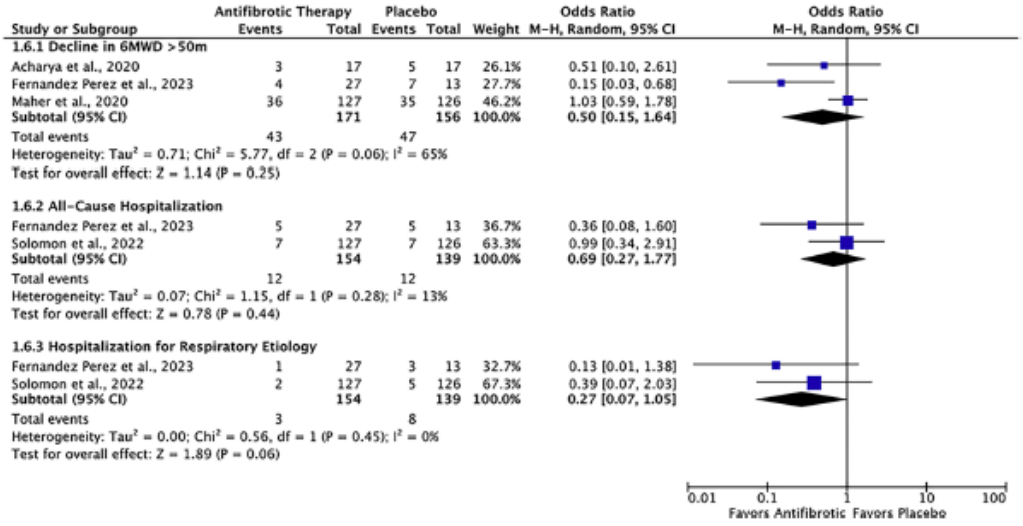


Fig. 4. Forrest plot of non-IPF PF-ILD patients divided into anti-fibrotic versus placebo groups. The outcomes of six-minute walk distance decline by more than 50 m, all-cause hospitalization, and hospitalization for respiratory etiology were assessed. The odds ratio was calculated by the Mantel-Haenszel method with a random-effects model.
Abbreviations: CI, confidence interval; MH, Mantel-Haenszel; 6MWD: six-minute walk distance.

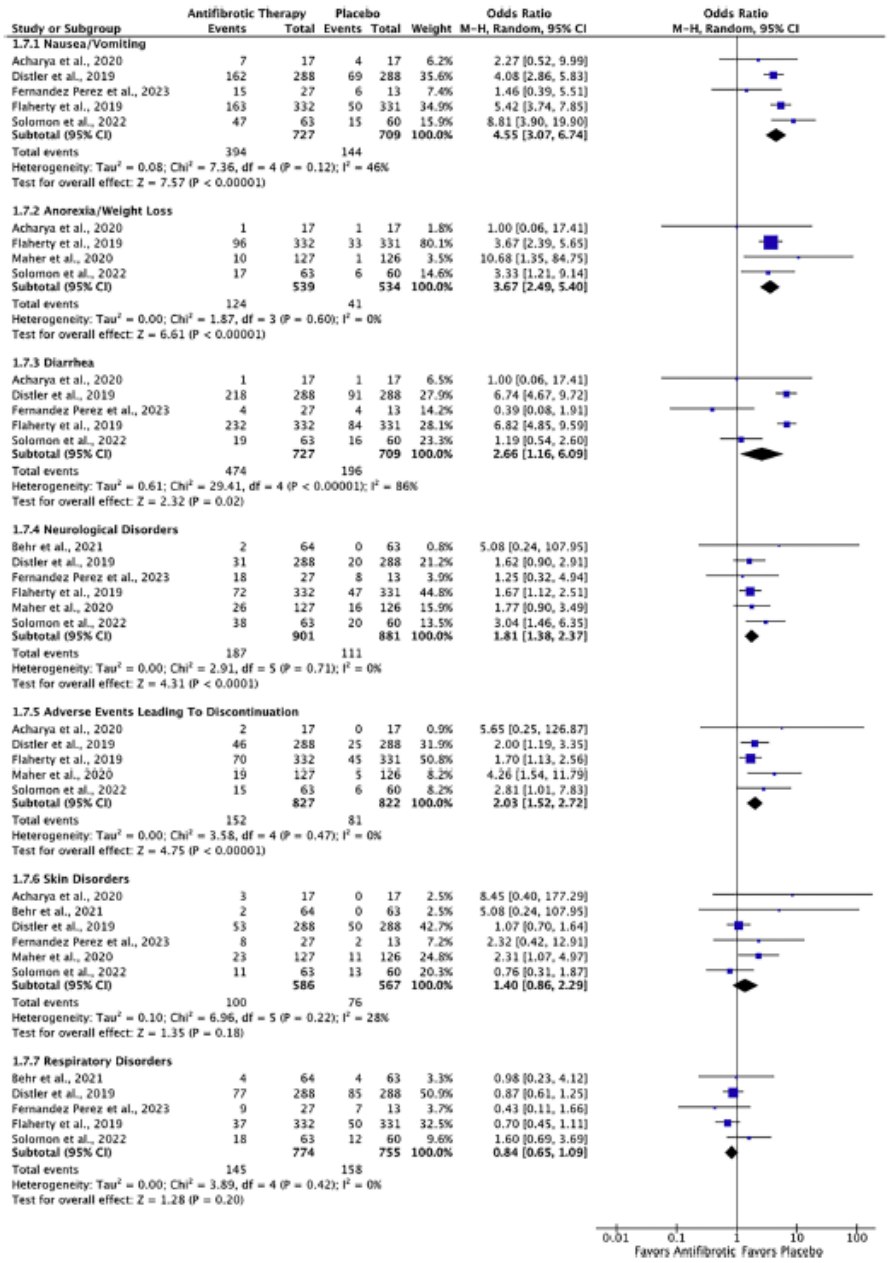


Fig. 5. Forrest plot of non-IPF PF-ILD patients divided into anti-fibrotic versus placebo groups. The adverse events of nausea/vomiting, anorexia/weight loss, diarrhea, neurological, adverse events leading to discontinuation of therapy, skin and respiratory disorders were assessed. The odds ratio was calculated by the Mantel-Haenszel method with a random-effects model.
Abbreviations: CI, confidence interval; MH, Mantel-Haenszel.

Anmerkung/Fazit der Autoren

In summary, the findings of our meta-analysis add to the existing literature that the use of anti-fibrotic therapy can reduce the decline in lung function based on FVC in non-IPF PF-ILD patients and can be considered as part of treatment. On a parallel level to IPF, continued improvement in the standard of clinical care, symptoms, and quality of life will occur with the increased understanding of the pathogenesis of non-IPF PF-ILD along with numerous pharmacological therapies being actively investigated and the emergence of multiple RCTs being conducted.

Lee J et al., 2025 [4].

Effectiveness of antifibrotics on health-related quality of life in patients with interstitial lung disease: a systematic review and meta-analysis

Fragestellung

We aimed to evaluate whether antifibrotic agents improve HRQoL and their effectiveness in treating HRQoL-related symptoms in patients with ILD.

Methodik

Population:

- patients diagnosed with ILD aged 18 years or older

Intervention:

- pirfenidone or nintedanib

Komparator:

- placebo

Endpunkte:

- HRQoL measures
  - HRQoL outcomes were assessed using the St. George's Respiratory Questionnaire (SGRQ)

Recherche/Suchzeitraum:

- MEDLINE via PubMed, EMBASE, and Cochrane Library. The final search was performed on August 25, 2025.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias 2 tool for RCTs
- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 studies were published between 2011 and 2025, six were non-IPF studies

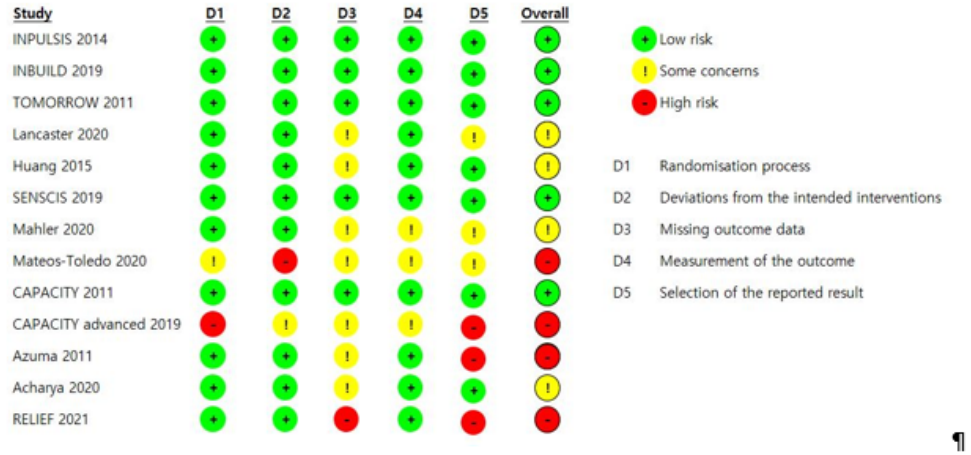
Charakteristika der Population/Studien:

Table 1. Characteristics of the included studies.

Author, year and references	Study	Enrollment period	Design	ILD type	Intervention	Follow-up time (weeks)	Population		
							Number		Age
							Antifibrotics	Placebo	Antifibrotics
Richeldi et al., 2011[24]	TOMORROW	2007–2010	RCT	IPF	Nin 150 mg twice	52	85	85	65.4 ± 7.8
Noble et al., 2011[25]	CAPACITY	2006–2008	RCT	IPF	PFD 2403 mg/d	72	345	347	66.3 ± 8
Nathan et al., 2019[26]	CAPACITY advanced	2006–2008, 2011–2013	RCT	IPF	PFD 2403 mg/d	52	90	80	70 (46–80)
Azuma et al., 2011[27]	NA	2005–NA	RCT	IPF	PFD 1200/1800 mg/d	52	430	104	65.0 ± 6.7
Richeldi et al., 2014,[6] Taniguchi et al., 2016,[28] Azuma et al., 2017,[29] Kolb et al., 2017,[30] Xu et al., 2019,[31] Ryerson et al., 2019,[32] Richeldi et al., 2020[33]	INPULSIS	2011–2013	RCT	IPF	Nin 150 mg twice	52	638	423	66.6 ± 8.1
Flaherty et al., 2019,[8] Inoue et al., 2023[34]	INBUILD	2017–2019	RCT	PF-ILD	Nin 150 mg twice	52	332	331	65.2 ± 9.7
Distler et al., 2019,[35] Azuma et al., 2021,[36] Highland et al., 2021,[37] Kuwana et al., 2021,[38] Volkmann et al., 2022[39]	SENSCIS	2015–2018	RCT	SSc-ILD	Nin 150 mg twice	52	288	288	54.6 ± 11.8
Huang et al., 2015[40]	NA	2012–2013	RCT	IPF	PFD 1800 mg/d	48	38	38	59.0 ± 5.94
Lancaster et al., 2020[41]	NA	2013–2014	RCT	IPF	Nin 150 mg twice	24	56	57	68.8 ± 7.6
Maher et al., 2020[42]	NA	2017–2018	RCT	PF-ILD	PFD 2403 mg/d	24	127	126	70 (61–76)
Acharya et al., 2020[43]	NA	2017–2018	RCT	SSc-ILD	PFD 600–2400 mg/d	24	17	17	42 (26–55)
Mateos-Toledo et al., 2020[44]	NA	2015–2017	RCT	cHP	PFD 900 mg twice	48	13	9	55 ± 7
Behr et al., 2021[9]	RELIEF	2016–2018	RCT	PF-ILD	PFD 267 mg, 534 mg, 801 mg tid	48	64	63	63.2 ± 10.6

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) except for (*) mmol/min/kPa.
ATAQ-IPF, A Tool to Assess Quality of Life in idiopathic pulmonary fibrosis; BDI-TDI, Baseline Dyspnea Index-Transition Dyspnea Index; cHP, chronic hypersensitivity pneumonitis; DLco, diffusing capacity for carbon monoxide; EQ-VAS, EuroQol-visual analog scale; F, H-J, Fletcher, Hugh-Jones; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; K-BILD, King's Brief Interstitial Lung Disease; NA, not available; Nin, nintedanib; PFD, pirfenidone; PF-ILD, progressive fibrosing interstitial lung disease; PROMs, patient-reported outcome measures; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire; SSc-ILD, systemic sclerosis-associated interstitial lung disease; UCSD-SOBQ, University of California, San Diego Shortness of Breath Questionnaire. Impact of antifibrotics on HRQoL; TID, ter in die.

Qualität der Studien:



Supplementary·Figure·6.·Quality·assessment·of·RCT·studies·using·the·ROB2·tool.·PFD,·pirfenidone;·RCT,·randomized·controlled·trial;·ROB,·risk·of·bias.¶

Studienergebnisse:

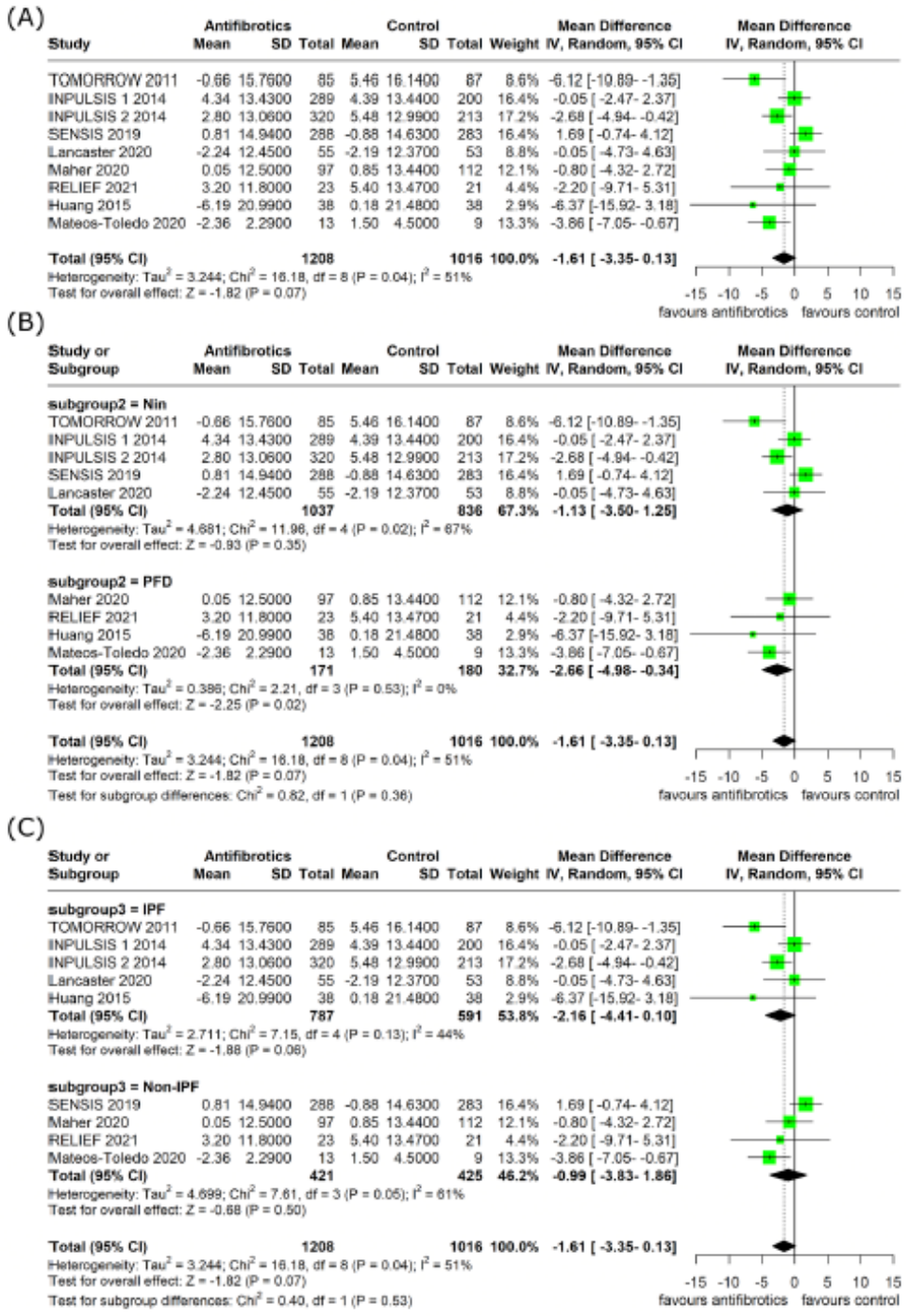


Figure 2. Forest plot presenting the pooled mean difference in total SGRQ scores between antifibrotic and non-antifibrotic groups. (a) Overall analysis; (b) Comparison between nintedanib and pirfenidone; (c) Comparison between IPF and non-IPF ILD.

CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IV, inverse variance; Nin, nintedanib; PFD, pirfenidone; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

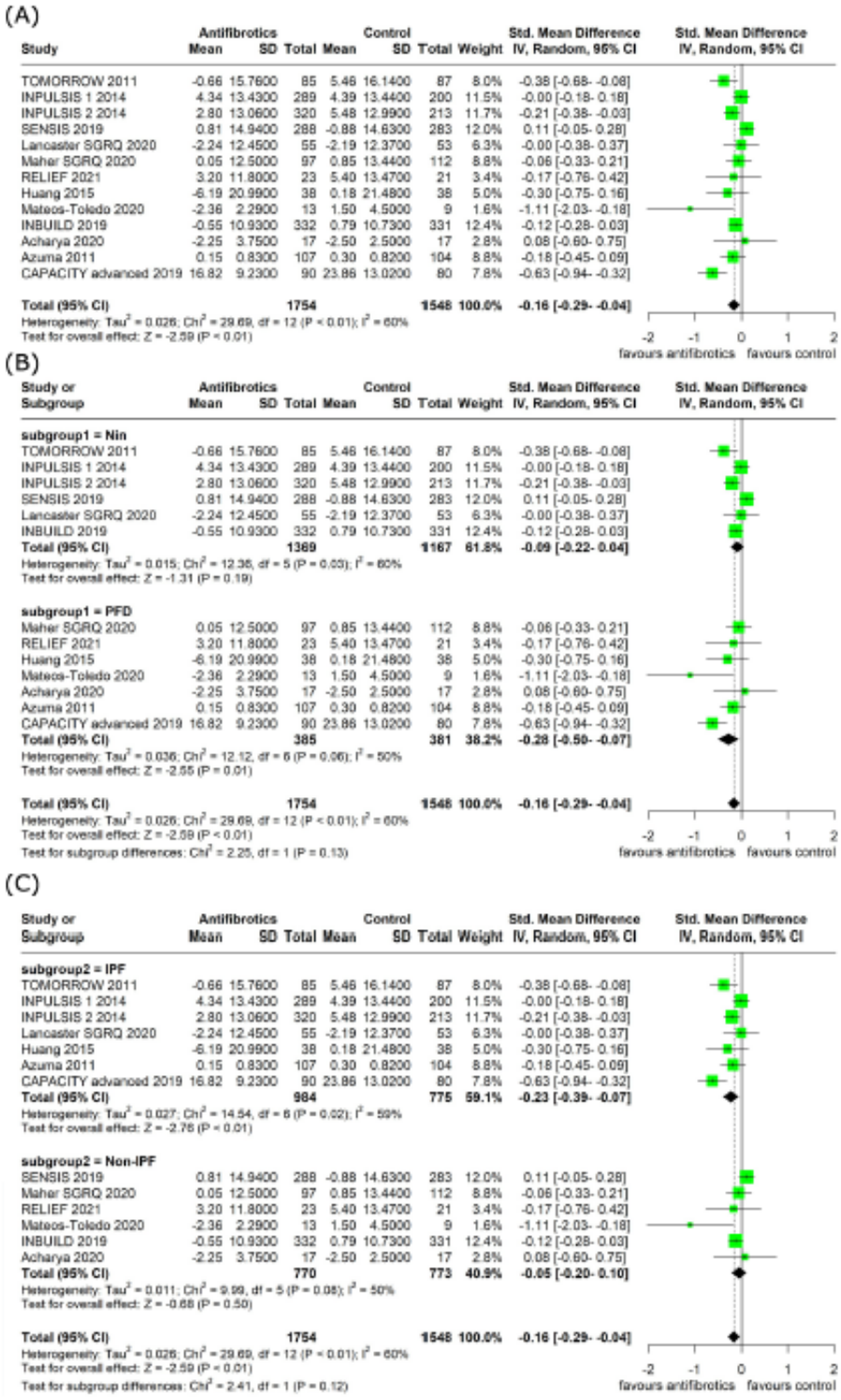


Figure 3. Forest plot presenting the pooled standardized mean difference in dyspnea scales between antifibrotic and non-antifibrotic groups. (a) Overall analysis; (b) Comparison between nintedanib and pirfenidone; (c) Comparison between IPF and non-IPF ILD.
CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IV, inverse variance; Nin, nintedanib; PFD, pirfenidone; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; Std., standard; UCSD-SOBQ, University of California, San Diego Shortness of Breath Questionnaire.

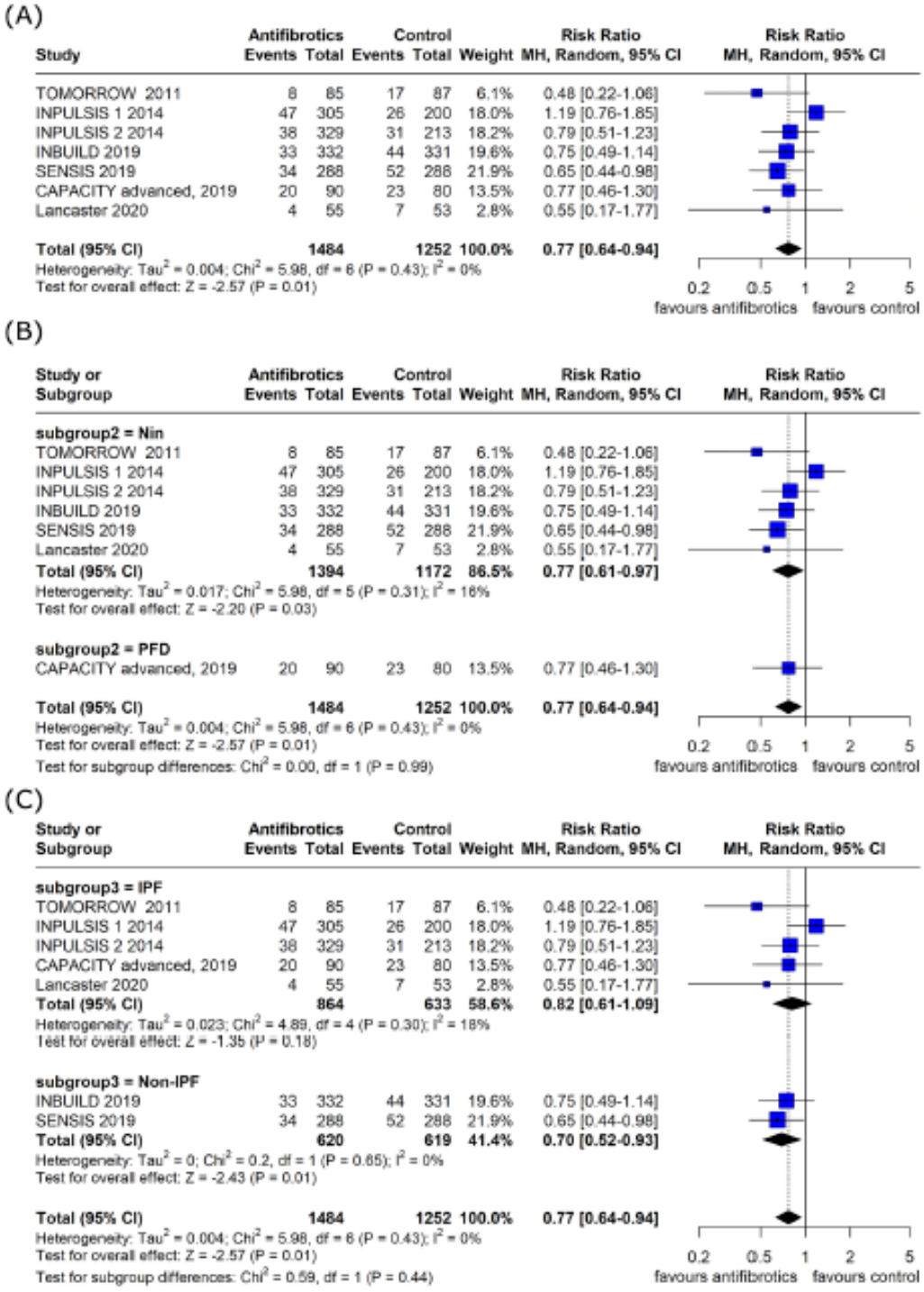


Figure 4. Forest plot presenting the pooled relative risk for cough symptoms between antifibrotic and non-antifibrotic groups. (a) Overall analysis; (b) Comparison between nintedanib and pirfenidone; (c) Comparison between IPF and non-IPF ILD.
CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MH, Mantel-Haenszel; Nin, nintedanib; PFD, pirfenidone.

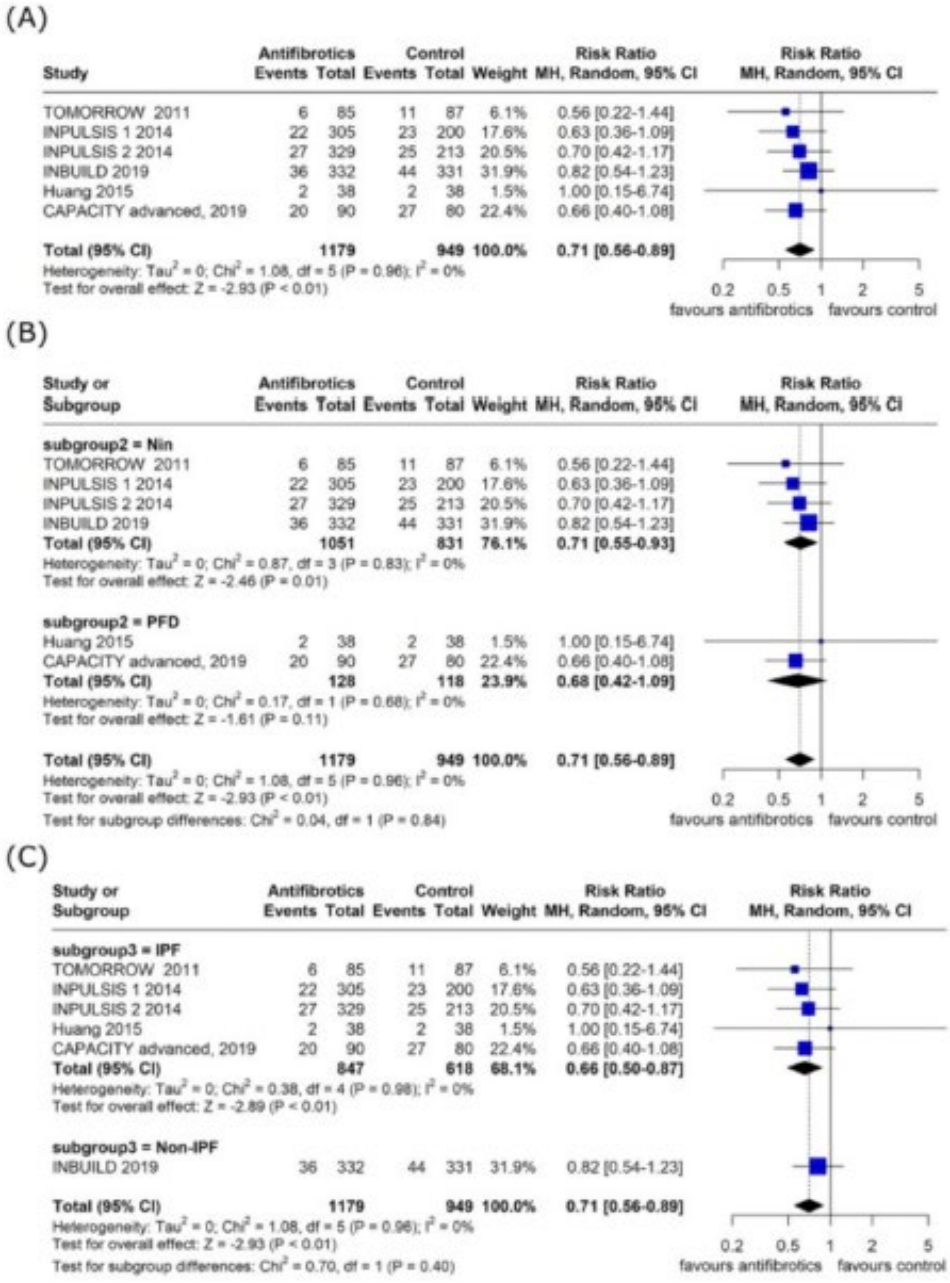


Figure 5. Forest plot presenting the pooled relative risk for dyspnea symptoms between antifibrotic and non-antifibrotic groups. (a) Overall analysis; (b) Comparison between nintedanib and pirfenidone; (c) Comparison between IPF and non-IPF ILD.
CI, confidence interval; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MH, Mantel-Haenszel; Nin, nintedanib; PFD, pirfenidone.

Anmerkung/Fazit der Autoren

Our meta-analysis suggests that antifibrotics may have a beneficial impact on HRQoL-related symptoms—particularly dyspnea and cough— with low-to-moderate certainty of evidence. By contrast, the effect on overall HRQoL totals remains uncertain (very low certainty), and fatigue appears to increase, requiring careful monitoring. The effectiveness was more pronounced in patients with fibrotic ILDs. These findings indicate potential benefits of antifibrotic therapy for improving patients' well-being, while underscoring the need for further high-quality studies to clarify its impact on HRQoL.

3.3 Leitlinien

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V., 2022 [2, 3]

Pharmakotherapie der idiopathischen Lungenfibrose (ein Update) und anderer progredienter pulmonaler Fibrosen (S2k-Leitlinie)

Zielsetzung/Fragestellung

konsentierte Aussagen zur Diagnostik und Verlaufsform der verschiedenen interstitiellen Lungenerkrankungen so zu treffen, dass die verfügbaren therapeutischen Strategien bei den jeweiligen Patientenpopulationen in optimaler Weise zum Einsatz kommen.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund der Relevanz für den deutschen Versorgungskontext wird die Leitlinie ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium, unklar, ob ein Methodiker teilgenommen hat;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Unklar, ob eine systematische Suche, Auswahl und Bewertung der Evidenz erfolgte;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- PubMed im Zeitraum 01.01.2018 bis 31.05.2022

LoE

- Keine Angaben

GoR

Stärke der Empfehlung	Sprachliche Formulierung
Starke Empfehlung	Soll/Soll nicht
Schwache Empfehlung	Sollte/sollte nicht
Empfehlung offen	Kann erwogen/verzichtet werden

>75% Konsens, > 95% starker Konsens// Mehrheitliche Zustimmung > 50%, kein Konsens <50%.

Sonstige methodische Hinweise

- Die Leitlinie ist ein Update.

Empfehlungen

1. Präambel: Definitionen: IPF; PPF (PF-ILD);

[…] Die deutsche Leitliniengruppe schließt sich der vorgeschlagenen Nomenklatur "Progrediente Pulmonale Fibrose" (Progressive Pulmonary Fibrosis, PPF) an und betont, dass dieser Begriff synonym zu verstehen ist mit dem bisherigen Begriff der PF-ILD, der

auch im Zulassungstext der EMA verwendet wurde. Die deutsche Leitliniengruppe beurteilt die in der internationalen Leitlinie vorgeschlagene Definition der Progression als zu eng gefasst, insbesondere, weil sie wichtige klinische Indikatoren der Progression außer Acht lässt und weil eine Lungenfunktionsprüfung zur Erfüllung der funktionellen Kriterien bei einigen Patienten, z. B. nach einer Exazerbation, gar nicht mehr durchgeführt werden kann, obwohl eindeutig eine Progression vorliegt. Dadurch könnten relevante Patientengruppen von einer für sie vorteihaften antifibrotischen Therapie ausgeschlossen werden, weil sie die Progressionskriterien nicht mehr erfüllen können.

Aus Sicht der Leitliniengruppe müssen folgende Voraussetzungen für die Einleitung einer antifibrotischen Therapie bei einer PPF erfüllt sein:

1. Im HRCT muß eine fibrosierende ILD vorliegen, die mindestens 10 % des Lungenparenchyms erfasst hat.
2. Für den Nachweis der Progression muß eine klinische, funktionelle oder röntgen-morphologische Verschlechterung während eines angemessenen Zeitraums innerhalb von 24 Monaten vorliegen. In Anlehnung an die Zulassungs-relevante INBUILD-Studie gelten orientierend folgende Kriterien:

   entweder • ein relativer Abfall der FVC ≥ 10 %

   oder Nachweis von mindestens zwei der folgenden Kriterien:1. Zunahme der respiratorischen Symptome 2. Relativer FVC-Abfall von ≥ 5 % des Sollwertes

3. Zunahme der Fibrosezeichen im HRCT *
4. Absoluter Abfall der DLco um ≥ 15 % des Sollwertes (DLco)
5. Einleitung einer Langzeitsauerstofftherapie bei Belastung oder in Ruhe oder dauerhafte Steigerung des Sauerstoffflusses einer bereits bestehenden Langzeitsauerstofftherapie um mindesten 1 l / min nach Maßgabe der aktuellen Langzeit-Sauerstofftherapie Leitlinie [18].
6. Stationäre Behandlung in Folge zunehmender Atembeschwerden bzw. wegen einer akuten Exazerbation der ILD
7. Abnahme der Gehstrecke im 6-Minuten-Gehtest um ≥ 50 m oder 20 % und / oder Abnahme der minimalen Sauerstoffsättigung während des 6-Minuten-Gehtests um > 5 % und unter 88 % absolut bei Raumluftatmung bzw. konstanter Sauerstoffflussrate

* Radiologische Fibrosezeichen definiert als:

- Zunahme von Ausmaß oder Schweregrad von Traktionsbronchi(ol)ektasen
- Neu auftretende Milchglasverschattung mit Traktionsbronchiektasen
- Neu auftretende feine Retikulationen
- Zunahme von Ausmaß oder Deutlichkeit von Retikulationen
- Neuauftreten oder Zunahme von Honigwaben
- Zunehmender Volumenverlust von Lungenlappen

Dieser Vorschlag fasst nach Ansicht der Leitliniengruppe die in Studien erfolgreich eingesetzten und die klinisch plausiblen Kriterien zusammen und schließt keine Patientengruppe aus. Durch das Eingangskriterium eines Befalls von mindestens 10 % des Lungenparenchyms durch einen fibrosierenden Lungengerüstprozess wird zusätzlich die Progressionswahrscheinlichkeit erhöht. Die Leitliniengruppe betont außerdem, dass jedes dieser Kriterien nur valide ist und damit als Indikator einer progredienten Fibrose angewendet werden darf, wenn zuvor andere Ursachen einer Verschlechterung ausgeschlossen wurden. Auszuschließende Ursachen einer klinischen Verschlechterung

sind insbesondere die Linksherzinsuffizienz mit pulmonalvenöser Stauung, die Entstehung einer pulmonalen Hypertonie, eine Überwässerung infolge Herz- oder Niereninsuffizienz und Infektionen.

2. Diskussion und Wertung einzelner medikamentöser Verfahren

2.6. Sollen PPF-Patienten antiinflammatorisch behandelt werden?

2.6.1. Nicht-autoimmune PPF

E6	Empfehlung
⇑⇑	Nicht-autoimmune PPF-Patienten sollen antiinflammatorisch behandelt werden, wenn Hinweise für die Beteiligung einer entzündlichen Komponente an der Progredienz der Lungenfibrose vorliegen und weitere Maßnahmen, wie z. B. Antigen- oder Expositionskarenz berücksichtigt wurden. Die Therapieeinleitung soll im ILD-Board festgelegt werden.
	Konsensstärke: 100 %

2.6.2. Autoimmune PPF

2.6.2.2. Rheumatoide Arthritis-assoziierte ILD (RA-ILD)

E7	Empfehlung
⇑	Die fortschreitende RA-ILD sollte antiinflammatorisch behandelt werden. Die Auswahl der Therapie soll im ILD-Board festgelegt werden.
	Konsensstärke: 100 %

2.6.2.3. Sjögren-assoziierte ILD

E8	Empfehlung
⇑	Die fortschreitende Sjögren-ILD sollte antiinflammatorisch behandelt werden.
	Konsensstärke: 100 %

E9	Empfehlung
⇑⇑	Die Auswahl der Therapie soll im ILD-Board festgelegt werden.
	Konsensstärke: 100 %

E10	Empfehlung
⇔	Bei nachgewiesener follikulärer Komponente bzw. Ansammlungen von Sekundärlymphfollikelbildungen kann eine B-Zell modulierende Therapie erfolgen.
	Konsensstärke: 100 %

2.6.2.4. Myositis-assoziierte ILD (MA-ILD)

E11	Empfehlung
⇑	Eine antiinflammatorische Therapie sollte bei fortschreitender MA-ILD durchgeführt werden. Die Auswahl der Therapie soll im ILD-Board festgelegt werden.
	Konsensstärke: 100 %

2.6.2.5. Systemische Sklerose (SSc)-assoziierte ILD

E12	Empfehlung
⇑	Patienten mit einer SSc-ILD sollten antiinflammatorisch behandelt werden.
	Konsensstärke: 100 %

E13	Empfehlung
⇑⇑	Die Auswahl der Therapie soll im ILD-Board festgelegt werden.
	Konsensstärke: 100 %

2.7. Sollen PPF-Patienten antifibrotisch behandelt werden?

2.7.2. Sollen PPF-Patienten mit Nintedanib behandelt werden?

E14	Empfehlung
⇑⇑	PPF-Patienten sollen mit Nintedanib behandelt werden. Die Therapieeinleitung soll im ILD-Board festgelegt werden.
	Konsensstärke: 100 %

2.7.3. Sollen PPF-Patienten (off-label) mit Pirfenidon behandelt werden?

E15	Empfehlung
⇑ ⇑⇑	PPF-Patienten sollten mit Pirfenidon behandelt werden, sofern eine antifibrotische Therapie mit Nintedanib sich als unzureichend wirksam erwiesen hat oder wegen Nebenwirkungen abgebrochen wurde. Die Therapieumstellung soll im ILD-Board festgelegt werden.
	Konsensstärke: 100 %

2.8. Sollen Patienten mit fibrosierender ILD (incl. IPF) und mit pulmonaler Hypertonie mit inhalativen Prostanoiden behandelt werden?

E16	Empfehlung
⇑⇑	IPF/PPF mit Hinweisen auf eine pulmonale Hypertonie sollen zur weiteren Abklärung und ggf. Therapieeinleitung in einem PH Zentren vorgestellt werden.
	Konsensstärke: 100 %

4. Diskussion und allgemeine Empfehlungen zur antifibrotischen Therapie bei der IPF und bei PPF

4.1. Wann sollte eine antifibrotische Therapie begonnen werden?

4.1.2. Bei PPF

E18	Empfehlung
⇑⇑	PPF-Patienten sollen antifibrotisch behandelt werde, wenn andere für die jeweilige Diagnose angemessene Behandlungen (z. B. anti-inflammatorische Therapie, Expositionskarenz) keine ausreichende Wirksamkeit gezeigt haben. Die individuelle Therapieentscheidung soll im ILD-Board festgelegt werden.
	Konsensstärke: 100 %

4.2. Wann sollte eine antifibrotische Therapie beendet werden?

4.2.2. Bei PPF

E22	Empfehlung
⇑⇑	Eine vom Patienten gut vertragene und die Progression verlangsamende antifibrotische Therapie soll zeitlich unbegrenzt, inkl. Therapiewechsel oder Studienteilnahme, ggf. bis zur Möglichkeit einer Lungentransplantation fortgeführt werden.
	Konsensstärke 100 %

E23	Empfehlung
⇑⇑	Wenn Nebenwirkungen trotz symptomatischer Therapie, Dosisreduktionen oder temporärer Behandlungsunterbrechungen nicht zu beherrschen sind, soll die Therapie beendet werden.
	Konsensstärke 100 %

E24	Empfehlung
⇑⇑	Die Entscheidung zum Therapieabbruch soll in Abstimmung mit dem Patienten getroffen werden.
	Konsensstärke 100 %

4.3. Wann sollte ein Therapiewechsel erfolgen?

4.3.2. Bei PPF

E28	Empfehlung
⇑	Bei PPF-Patienten sollte im Falle des Auftretens nicht beherrschbarer Nebenwirkungen oder einer unverminderten Progression unter Nintedanib ein Therapiewechsel auf Pirfenidon oder eine Studienteilnahme erwogen werden.
	Konsensstärke: 100 %

E29	Empfehlung
⇑⇑	Die Frage eines Therapiewechsels soll im ILD-Board entschieden werden.
	Konsensstärke: 100 %

4.4. Kann eine antifibrotische Kombinationstherapie sinnvoll sein?

E30	Empfehlung
⇓⇓	IPF- oder PPF-Patienten sollen nicht mit einer Kombinationstherapie aus Nintedanib und Pirfenidon außerhalb kontrollierter klinischer Studien behandelt werden
	Konsensstärke: 100 %

4.6. Wann sollte eine immunmodulatorische Therapie beendet werden?

E32	Empfehlung
⇑	Bei nicht-autoimmuner und autoimmuner PPF sollte eine antiinflammatorische Therapie beendet werden, wenn über eine angemessene Beobachtungszeit eine unverminderte Progredienz oder Komplikationen (v. a. Infektionen) bzw. nicht beherrschbare Nebenwirkungen auftreten.
	Konsensstärke: 100 %

E33	Empfehlung
⇑⇑	Bei autoimmuner PPF soll die Aktivität der Grunderkrankung und ihrer extrapulmonalen Manifestationen in die Entscheidung zur Therapiebeendigung einbezogen werden. Die Entscheidung zur Therapiebeendigung soll interdisziplinär, z. B. in einem ILD-Board, getroffen werden.
	Konsensstärke: 100 %

Raghu G et al., 2022 [6].

American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Asociacion Latinoamericana de Torax (ALAT)

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Zielsetzung/Fragestellung

to provide the basis for rational, informed decisions by clinicians.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Medline, Excerpta Medica Database (EMBASE), and Cochrane Database of Systematic Reviews. Searching was conducted in July 2020

LoE

- Grading, Recommendations, Assessment, Development, and Evaluation (GRADE)

GoR

Table 2. Implications of the Guideline Recommendations

	Strong Recommendation ("We Recommend…")	Conditional Recommendation ("We Suggest…")
From the GRADE working group		
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action, and only a small minority would not.	The majority of individuals in this situation would want the suggested course of action, but a sizable minority would not.
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for different patients, and you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
For policy makers	The recommendation can be adapted as policy in most situations, including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary among regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.
Additional conceptualization from the ATS/ERS/JRS/ALAT Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis Guidelines panel discussion		
	It is the right course of action for >95% of patients.	It is the right course of action for >50% of patients.
	"Just do it."	"Slow down, think about it, discuss it with the patient."
	You would be willing to tell a colleague who did not follow the recommendation that he/she did the wrong thing.	You would not be willing to tell a colleague who did not follow the recommendation that he/she did the wrong thing; it is "style" or "equipoise."
	The recommended course of action may be an appropriate performance measure.	The recommended course of action is not appropriate for a performance measure.

- Three outcomes were possible: 1. Greater than 20% abstentions indicated that the course of action could not be addressed. When the primary reason for the abstentions was insufficient evidence, a research recommendation was made. 2. Fewer than 20% abstentions with greater than 70% agreement on the appropriate course of action yielded a graded recommendation or suggestion. 3. Fewer than 20% abstentions with less than 70% agreement on the appropriate course of action yielded no recommendation due to insufficient agreement among the committee regarding the most appropriate course of action. If additional evidence is likely to resolve the lack of agreement, a research recommendation was made.

Recommendations

Part II: Diagnosis and Treatment of PPF in Fibrotic ILD, Other than IPF

Definition of PPF

Table 4. Definition of Progressive Pulmonary Fibrosis

Definition of PPF
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:
1 Worsening respiratory symptoms
2 Physiological evidence of disease progression (either of the following): a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up
3 Radiological evidence of disease progression (one or more of the following): a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.
*Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in D_{LCO} given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

Evidence-based Recommendations for Treatment of PPF, Other than IPF

Pirfenidone.

We recommend further research into the efficacy, effectiveness, and safety of pirfenidone in both 1) non-IPF ILD manifesting PPF in general and 2) specific types of non-IPF ILD manifesting PPF.

SUMMARY OF EVIDENCE. The systematic review that informed the committee's recommendation is published independently (162); we summarize the salient findings. The systematic review identified two randomized trials that enrolled patients with PPF and evaluated the effects of
pirfenidone (127, 128). One trial of uILD randomly assigned 253 patients with fibrotic uILD to receive pirfenidone or placebo, then followed themfor 24 weeks (128). The other trial (RELIEF) randomly assigned 127 patients with PPF to receive pirfenidone or placebo, then followed themfor 48 weeks (127). The latter trial included patients with chronic HP, CTD-related ILD, NSIP, and asbestosis-induced lung fibrosis. The trial was terminated early because of futility triggered by slow recruitment; however, imputations were conducted formissing data with the primary analysis favoring the pirfenidone arm. Disease progression. When the trials were aggregated by meta-analysis, pirfenidone reduced the decreases in FVC by 100 ml and in percentage predicted FVC by 2.3% over 24 weeks (127, 128). In the uILD trial, pirfenidone decreased by 1.6 times the likelihood that percentage predicted FVC would decline.5% and decreased by 1.9 times the likelihood that percentage predicted FVC would decline.10% (128). Mortality. The uILD trial did not demonstrate a statistically significant difference in progression-free survival (128). Similarly, the RELIEF trial did not show a statistically significant difference in progression-free survival ormortality at 48 weeks (127). Lung function. Only the RELIEF trial reported changes in FEV1 and TLC, neither of which was statistically significant (127). The RELIEF trial showed that pirfenidone reduced themean decrease in DLCO by 0.40 mmol/kPa/min (127), while the uILD trial found that patients with fibrotic uILD who received

pirfenidone had a 3.7- times reduced risk of a DLCO decline of .15%, although there was no statistically significant difference in themean change in percentage predicted DLCO (128).When the trials were combined by meta-analysis, pirfenidone attenuated the decline in 6MWD by 25.2m, whereas in the uILD trial the number of patients whose 6MWD declined by.50 mwas unchanged (127, 128). Respiratory symptoms. There was no significant difference in mean St. George's Respiratory Questionnaire score, Leicester Cough Questionnaire score, UCSD-SOBQ scores, or visual analog scale score for cough (127, 128). AEs. Pirfenidone increased the risk of gastrointestinal discomfort 1.8 times and photosensitivity 4.9 times. Pirfenidone increased the risk of any AE 1.2 times and the risk of treatment-related AEs 1.5 times (128). Quality of evidence. The quality of evidence for all outcomes was rated as very low, meaning that the committee should have very low confidence in the estimated effects, and therefore, the effects summarized below should be interpreted with caution. Themain reason for the very lowquality rating was that although there were two randomized trials, one trial was terminated early because of futility, and both trials were limited by small sample sizes, resulting in confidence intervals whose ends included both benefit and harm.

Referenzen:
162. Ghazipura MHT, Mammen MJ, Bissell B, Macrea M, Herman D, Hon SM, et al. Pirfenidone in progressive pulmonary fibrosis. Ann Am Thorac Soc (In press)
127. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F, et al. RELIEF Investigators. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med 2021;9:476–486.
128. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med 2020;8:147–157.

Nintedanib.

We suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF (conditional recommendation, low quality evidence).

Remarks: Standard management will differ from patient to patient. In many patients it will be immunosuppressive treatment in an attempt to stabilize or reverse initial disease, but this is not a prerequisite, as in some patients, standard management could be antigen remediation or observation. Besides this, it should be acknowledged that in many ILDs, evidence-based guidance for standard of care is lacking; hence, standard of care may vary from region to region.

We recommend research into the efficacy, effectiveness, and safety of nintedanib in specific types of non- IPF ILD manifesting PPF.

SUMMARY OF EVIDENCE. The systematic review that informed the committee's recommendation is published independently (163); we summarize the salient findings. The systematic review identified one randomized trial (4) and a post hoc analysis of the trial (164). The randomized trial (INBUILD) randomly assigned 663 patients with PPF to nintedanibor placebo for 52 weeks, while the post hoc analysis compared the effects of nintedanib with placebo in the individual types of ILD that weremanifesting PPF. The type of ILD was determined by the investigators at each study site without prespecified diagnostic criteria being provided to the site investigators, rather than through a central review process, so diagnostic variation across institutions was possible. Disease progression. Among all patients with PPF, FVC declined in both the nintedanib and placebo arms of the INBUILD trial, but themean annual decline was significantly less (107ml) in the nintedanib arm. The trial also described "progression of ILD" as an AE without defining it in this context; however, nintedanib decreased the risk of this progression 2.4 times. The difference in the annual decline in FVCbetween the nintedanib and placebo arms was 128 ml/yr among patients who had a radiological UIP pattern, whereas it was 75.3 ml/yr among patients with a radiological non- UIP pattern (4). Nintedanib decreased the risk of progression of ILD as an AE 2.3 times among patients who had a radiological UIP pattern, but there was no significant difference among patients who had a radiological non-UIP pattern (4). Patients with PPF who received nintedanib had less annual decline in the FVC if their underlying ILD was CTDrelated ILD (106.2 ml/yr less), fibrotic NSIP (141.7 ml/yr less), or fibrotic occupational lung disease (252.8 ml/yr less); however, there was no significant difference in the progression of ILD as an AE for any type of ILD. Among patients with PPF due to fibrotic HP, sarcoidosis, or uILD, there was no difference in the annual decline in FVC or the progression of ILD as an AE. It is

noteworthy that the estimates are based on small sample sizes: CTD-related ILD, n = 147; fibrotic NSIP, n = 125; fibrotic occupational lung disease, n = 39; fibrotic HP, n = 173; sarcoidosis, n = 12; uILD, n = 114; and other, n = 53 (164). Mortality. The INBUILD trial showed no significant difference in all-cause mortality or fatal AEs among all patients with PPF. Similarly, there was no difference in all-cause mortality among patients with PPF who had a radiological UIP pattern (4). Mortality was not analyzed among patients with PPF who had a radiological non-UIP pattern (4) or for the type of underlying ILD (164). Adverse effects. Among all patients with PPF, nintedanib increased gastrointestinal AEs, including abdominal pain (4.2 times), nausea (3.1 times), vomiting (3.6 times), diarrhea (2.8 times), anorexia (2.8 times), weight loss (3.7 times), elevated aspartate aminotransferase (3.2 times), elevated alanine aminotransferase (3.6 times). It also increased the likelihood of any AE (1.1 times), an AE leading to permanent dose reduction (7.9 times), and an AE leading to treatment discontinuation (1.9 times). There were no significant differences in respiratory AEs (including cough, dyspnea, bronchitis, and nasopharyngitis), headache, serious AEs, or severe AEs (4). The finding of more AEs in the nintedanib arm was seen regardless of whether patients had a radiological UIP pattern or non-UIP pattern (4) and regardless of the type of underlying ILD (164), although there was slight variation among groups in which AEs were positive.
Quality of evidence. The quality of evidence for all outcomes was rated as low, meaning that the committee had low confidence in the estimated effects, and therefore, the effects summarized below should be interpreted with caution. The overall low-quality rating is based on the lowest quality of evidence rating among the two critical outcomes; the quality of evidence was moderate for disease progression but low for mortality because there was a single randomized trial with a small number of events, resulting in confidence intervals whose ends included both benefit and harm.

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Piotrowski W et al., 2022 [5].

Polish Respiratory Society (PTChP)

Guidelines of the Polish Respiratory Society on the Diagnosis and Treatment of Progressive Fibrosing Interstitial Lung Diseases Other than Idiopathic Pulmonary Fibrosis

Zielsetzung/Fragestellung

Objectives of the guidelines:

- To improve the quality and reliability of the diagnosis of progressive fibrosis in the course of interstitial lung diseases other than IPF;
- To increase access to anti-fibrotic therapy by promoting diagnostic and eligibility criteria for treatment in Poland;
- To identify health needs and deficiencies in the care of patients with progressive fibrosis in the course of interstitial lung diseases other than IPF

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium, unklar ob Patientenvertreter beteiligt waren;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren teilweise dargelegt;

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz sind über Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- A review of the available literature was conducted based on the Medline and Cochrane databases. The literature search was terminated on 31 December 2021

LoE

- GRADE
- The quality of evidence was assessed as high, moderate, low, and very low

GoR

- The strength of recommendations was assessed as strong or conditional

Sonstige methodische Hinweise

- The main methodical problem, which is particularly significant in the context of the assessment of the quality of evidence, is the classification of the analyzed group of diseases. Namely, progressive fibrosis in interstitial lung diseases other than IPF is defined through the exclusion of a group of diseases with a shared phenotype of progressive pulmonary fibrosis that does not meet the diagnostic criteria for IPF, a that is disease strictly defined in line with current guidelines. This division results in a large number of disease entities representing this group of diseases, as well as a considerable heterogeneity, resulting in methodological imperfections and consequent difficulties in their synthesis
- We also decided to stay with the term “progressive fibrosing ILD, PF-ILD” that is currently used worldwide, instead of changing it to PPF, as proposed by the authors of the most recent international guidelines

Treatment Recommendation

Recommendation 1:
We recommend that an opinion of a multidisciplinary team should be considered in the management of patients with interstitial lung disease in the course of systemic autoimmune diseases.

Evidence quality: very low
Strength of recommendation: strong
(voting results: strongly for—22 votes, conditionally for—5 votes, abstain from voting—0 votes, conditionally against—2 votes, strongly against—0 votes)

Commentary: *Systemic autoimmune diseases are associated with extrapulmonary manifestations, which often represent a comparable or more significant clinical problem than manifestations of respiratory involvement. Therefore, in these cases, an opinion made by an experienced clinician, rheumatologist, and, depending on the needs, other specialists is necessary.*

Background:
Given the broad spectrum of ILDs and their differentiation in terms of etiology, pathogenesis, clinical presentation, and long-term prognosis, AI-ILD and interstitial pneumonia with autoimmune features (IPAF) deserve special attention in this aspect. Interstitial patterns in these entities may include NSIP, UIP, OP, or LIP. Immunosuppressants and glucocorticosteroids used in the treatment of systemic autoimmune disease may insufficiently control the course of an ILD. Moreover, anti-fibrotic drugs do not affect extrapulmonary manifestations [23]. On the other hand, as demonstrated in the SENSCIS study, the combination of an anti-fibrotic with a mycophenolate mofetil may provide beneficial effects on slowing the rate of progression of interstitial lung fibrosis [23]. The development of the optimal treatment regimen should be the result of a joint discussion of the representatives of various specialists—in this case, a pneumonologist and rheumatologist with appropriate clinical experience. Consideration should be given to the possibility of combining drugs of different pharmacologic classes; a decision on optimal treatment

(if monotherapy is considered) must be made, or treatment should be discontinued if an MDD asserts that the treatment will not bring the expected benefits and potential adverse effects will worsen the quality of life. Making these decisions is particularly difficult given the lack of data on potential interactions between different drug groups [78–80]. In the event of such doubts, the composition of the multidisciplinary team should be extended to include a clinical pharmacologist. Agreeing on the optimal treatment regimen, examinations, and follow-up visits is also a task for the multidisciplinary team [4,16,81]. Decisions on non-pharmacological treatment (palliative care, lung transplantation) may require the participation of specialists in the relevant fields.

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Recommendation 2:
We suggest that a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF should be treated with first-line therapy dedicated to the diagnosed underlying disease.

Evidence quality: very low
Strength of recommendation: conditional
(voting results: strongly for—12 votes, conditionally for—12 votes, abstain from voting—5 votes, conditionally against—0 votes, strongly against—0 votes)

Commentary: *Treatment of the underlying disease—in particular, diseases in which the respiratory system is just one possible manifestation—may have a potentially beneficial effect on the course of interstitial lung disease and improve long-term prognosis. The results of single randomized clinical trials indicate efficacy in limiting AI-ILD progression.*

Background:
A progressive interstitial pulmonary fibrosis phenotype other than IPF occurs in different disease entities, such as HP, AI-ILD, iNSIP, and uILD [65,82]. Fibrosis in PFILD is often preceded by or related to activation of various inflammatory and fibrotic pathways that may lead to fibroblast activation and differentiation into myofibroblasts, producing an extracellular matrix, which results in the remodeling of the lung parenchyma and leads to pulmonary fibrosis [83]. In the treatment of these ILDs, glucocorticosteroids or immunosuppressants (e.g., cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab) are used. The impact of immunosuppression on PF-ILD is largely unknown, except for ILD in systemic sclerosis (SSc-ILD) [84]. Randomized clinical trials of SSc-ILD showed that cyclophosphamide-treated patients achieved a slower decline in FVC after one year of treatment compared to the placebo group, and a study assessing the efficacy of two years of mycophenolate mofetil (MMF) treatment vs. cyclophosphamide treatment showed that the effects of the two drugs were comparable, with lower toxicity of MMF [85,86]. Immunomodulatory treatment of the underlying disease may be of major importance, particularly in autoimmune diseases, which should take into account not only respiratory effects, but also the overall disease activity and inflammatory processes in other organs and tissues [87]. In the treatment of HP, the first necessary step is to identify and eliminate the causal antigen, which has a positive impact on the course of the disease and prognosis [4,34]. Early immunomodulatory treatment in patients with fibrosing NSIP or HP may be associated with improved respiratory function and a favorable long-term prognosis [19,20]. MMF and azathioprine are considered first-choice drugs in patients with fibrosing HP who present

with disease progression despite previous glucocorticoid therapy [83]. A study evaluating the effect of MMF or azathioprine on lung function in patients with chronic HP demonstrated that both drugs were well tolerated and reduced the need for prednisone, and that annual treatment significantly improved $T_{L,CO}$ [88]. However, it should be noted that other studies showed opposite results [89,90].

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Recommendation 3:
We recommend that in a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF, anti-fibrotic therapy with nintedanib should be used in the event of ineffectiveness of the therapy recommended for the treatment of the underlying disease.

Evidence quality: low
Strength of recommendation: strong
(voting results: strongly for—16 votes, conditionally for—10 votes, abstain from voting—2 votes, conditionally against—1 vote, strongly against—0 votes)

Commentary: *This recommendation promotes the use of nintedanib as the only treatment option currently available.*

Background
Treatment of ILDs other than IPF with a predominant component of inflammation from the point of view of the disease pathobiology is currently based on immunomodulatory therapy (glucocorticoids or immunosuppressants) and elimination of known causal factors in occupational or environmental diseases [4,91]. In practice, decisions on optimal immunomodulatory treatment are driven mainly by the diagnosis of the underlying disease and its course. Nevertheless, a considerable percentage of patients will, despite the use of immunomodulatory therapy recommended for the treatment of the underlying disease, develop PF-ILD, regardless of the initial diagnosis of an ILD. In these cases, from the point of view of pathobiology, the dominant factor is the process of fibrosis, rather than inflammation, and at the same time, this determines the progression of the disease, although the specific mechanisms responsible for the development of this phenotype are not known [92]. In this situation, immunomodulatory treatment is likely ineffective in terms of ILD control and is unable to prevent further worsening of the patient's clinical

condition. A recently completed randomized phase III INBUILD clinical trial demonstrated the efficacy and safety of anti-fibrotic therapy with nintedanib in the population of patients with PF-ILDs other than IPF [16]. The benefits of nintedanib were also demonstrated in both the overall study population and in subgroups of patients with UIP and non-UIP radiological patterns [16]. Even though the INBUILD study did not have the power to provide evidence in favor of nintedanib in specific diseases in a broad spectrum of PF-ILDs, its results suggest that nintedanib reduces the rate of progression of ILDs measured by the decline in FVC in patients with PF-ILDs, regardless of the initial ILD diagnosis [18]. At the same time, additional analyses of the study showed that concomitant use of glucocorticoids at the initiation of nintedanib treatment or the addition of other immunomodulatory therapies during treatment did not adversely affect the benefits of nintedanib in reducing the rate of decline in FVC [81], and the benefits were consistent regardless of the progression criterion used in the identification of the PF-ILD [93] or baseline FVC [94].

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Recommendation 4:
No recommendations were made for or against the use of anti-fibrotic therapy with pirfenidone if treatment of the underlying disease has failed in a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF.

Evidence quality: very low
Strength of recommendation: not issued
(voting results: strongly for—1 vote, conditionally for—12 votes, abstain from voting—14 votes, conditionally against—2 votes, strongly against—0 votes)

Commentary: *It should be noted that the lack of a recommendation does not mean a negative recommendation. Some patients with PF-ILDs other than IPF may benefit from pirfenidone treatment.*

Background
Pirfenidone is the first approved treatment for IPF [95–97]. Given its multifactorial anti-fibrotic effect, a similar effect may also be expected in patients with other ILDs with the progressive fibrosis phenotype. We have the results of several randomized clinical trials. The RELIEF study enrolled patients with progressive pulmonary fibrosis in AI-ILD, NSIP, fHP and asbestos exposure [98]. Most patients received standard treatment with glucocorticoids alone or in combination with an immunosuppressant. The study was terminated early due to too slow enrollment of eligible patients. The analysis of available data showed that patients receiving pirfenidone had a significantly lower FVC decline than patients receiving a placebo (difference between the groups of 1.69%, p = 0.042). No significant differences in progression-free survival were demonstrated, while a higher proportion ofpatients on pirfenidone maintained stable functional parameters (FVC decline of less than 5% over 48 weeks). The beneficial effects of pirfenidone were also observed with regard to $T_{L,CO}$ and distance in 6MWT [98]. The second phase (II), a multicenter, international, randomized, double-blind, placebo-controlled study, investigated the efficacy of pirfenidone in patients with unclassifiable ILDs with the progressive fibrosing phenotype [17]. The primary endpoint

was a change in FVC after 24 weeks of treatment as assessed by daily home spirometry. It was not achieved due to technical difficulties, irregularities, and lack of consistency in performing this examination by patients at home. However, the evaluation of office spirometry (secondary endpoint) showed a smaller decline in FVC in pirfenidonetreated patients as compared with the placebo (17.8 mL vs. 113.0 mL/24 weeks). Fewer patients in the pirfenidone group experienced FVC declines greater than 5 and 10% over the study duration. No differences in progression-free survival or quality of life were observed. Although the aforementioned studies did not meet formal requirements, they indicate the efficacy of pirfenidone in inhibiting pulmonary fibrosis progression, as in the case of IPF. No new safety signals were observed—the adverse event profile was consistent with the one observed in the studies in IPF patients [17,98]. Pirfenidone is currently being studied in patients with SSc-ILD, rheumatoid-arthritis-associated interstitial lung disease (TRAIL-1), sarcoidosis with pulmonary fibrosis, fHP, and pneumosilicosis [99].

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Recommendation 5:
We suggest using an anti-fibrotic agent as the first-choice treatment in certain clinical situations.

Evidence quality: very low
Strength of recommendation: conditional
(voting results: strongly for—7 votes, conditionally for—12 votes, abstain from voting—6 votes, conditionally against—4 votes, strongly against—0 votes)

Commentary: *Immunosuppressive therapy is ineffective and even harmful in patients with IPF. Some patients with interstitial fibrosis with a UIP pattern are unlikely to have a positive response to such treatment. In patients in whom fibrotic lung lesions predominate in the presentation or are the only manifestation of the disease, it is reasonable to initiate anti-fibrotic treatment without immunomodulatory treatment.*

Background
Currently, no studies are available that directly assess the efficacy of immunomodulatory treatment compared to anti-fibrotic therapy in patients with PF-ILDs. Treatment decisions in this group of patients are, therefore, difficult and should be supported by a discussion in a multidisciplinary team, considering close collaboration with a rheumatologist in the case of AI-ILD. Antifibrotic therapy as a first-choice therapy should be considered in patients with an IPF-like phenotype, i.e., patients with a UIP pattern in lung HRCT or histopathological examinations and presenting worsening respiratory symptoms, FVC decline _ 10% within 12 months, and especially in those patients for whom immunosuppressive therapy would be associated with greater potential adverse effects [83,100]. The presence of the UIP pattern in patients with RA-associated ILD or fibrotic HP is associated with a worse prognosis than in the case of other patterns visible in HRCT and histology [100,101]. A comparison of the placebo groups from the INPULSIS and INBUILD studies showed that the FVC decline was similar between IPF and PF-ILD patients with a similar pattern of UIP in HRCT [3]. Immunosuppressive therapy in patients with IPF was associated with poorer survival compared with the placebo [102,103]. Some retrospective studies also suggested the deleterious effects of immunosuppressive therapy in fHP [89,90]. Patients with fibrosing NSIP have a poorer prognosis than patients with the cellular disease [104]. Immunomodulatory treatment (glucocorticoids, MMF,

azathioprine, cyclophosphamide, rituximab) is the treatment of choice in NSIP patients according to the previous recommendations [104,105]. Antifibrotic agents were evaluated in randomized clinical trials in patients with PF-ILD and SSc-ILD, some of which included patients with fibrotic NSIP [16,23,37]. Studies with nintedanib have shown that it slowed the rate of decline in FVC by 57% in PF-ILD, with 19% being patients with NSIP, and by 44% in SSc-ILD, where NSIP was the predominant form of ILD [16,23]. Treatment with nintedanib, the only agent currently approved for the treatment of PF-ILD, should be considered in the case of fibrosis progression in patients with NSIP when immunosuppressive therapy is contraindicated.

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Recommendation 6:
We suggest that in a patient with a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF, one should consider simultaneous treatment with a disease-modifying drug and anti-fibrotic therapy.

Evidence quality: very low
Strength of recommendation: conditional
(voting results: strongly for—6 vote, conditionally for—17 votes, abstain from voting—5 votes, conditionally against—1 vote, strongly against—0 votes)

Commentary: *Taking into account the potential benefits of adding an anti-fibrotic agent to background therapy, such management should be considered in patients with PF-ILDs, particularly in patients with systemic autoimmune disease.*

Background
Immunosuppressive therapy remains the basis for the management of patients with PF-ILDs—in particular, autoimmune diseases, such as rheumatoid arthritis or systemic sclerosis. Glucocorticosteroids and certain immunosuppressive agents, such as MMF and azathioprine, are also used in the treatment of HP, NSIP, or uILD [14,106]. Despite such treatments, approximately 18 to 32% of patients with ILD other than IPF are estimated to develop a progressive fibrosing phenotype [14]. The results of randomized clinical trials in recent years show a beneficial effect of anti-fibrotic drugs on slowing the rate of progression of PF-ILDs [16,23,98]. Combining immunosuppressive and anti-fibrotic therapy may be a beneficial therapeutic option, taking into account the potential for both therapies to influence different pathogenic pathways involved in the development and progression of PF-ILDs. The safety of a combination treatment with pirfenidone and MMF, as well as nintedanib and MMF, was established in clinical trials in patients with uILD and SSc-ILD [17,23]. The SENSCIS study enrolled patients with SSc-ILD taking MMF at a stable dose in the previous 6 months, methotrexate, or _10 mg prednisone, and ultimately, around half of the patients were treated with MMF. It was observed that in the placebo group, the decline in FVC was lower in patients receiving MMF, suggesting a potentially beneficial effect of MMF. In addition, patients treated with both nintedanib and MMF had the slowest rate of FVC decline, suggesting a potential role for combination therapy in SSc-ILD [23]. In the INBUILD trial, immunosuppressant use was not allowed at randomization and for the next 6 months, except for prednisone at a dose of _20 mg/day. Post-study analysis showed that the use of glucocorticoids at baseline or the initiation of immunomodulatory treatment during the study had no impact on the beneficial effects of nintedanib in patients with PF-ILDs [81]. An SLS-III trial evaluating the efficacy and safety of the combination therapy with pirfenidone and MMF versus MMF alone in patients with SSc-ILD is ongoing [99].

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Recommendation 7:
No recommendations were made for or against termination of anti-fibrotic therapy in the case of noted progression during treatment of a progressive fibrosing interstitial lung disease (PF-ILD) other than IPF.

Evidence quality: very low
Strength of recommendation: not issued

(voting results: strongly for—4 votes, conditionally for—6 votes, abstain from voting—9 votes, conditionally against—8 votes, strongly against—2 votes)

Commentary: *In each case of PF-ILD progression, the decision should be made on an individual basis.*

Background
The results of the INBUILD study showed that anti-fibrotic therapy with nintedanib slowed the rate of FVC loss in a population of patients who developed progressive fibrosis (PF-ILD) in interstitial diseases other than IPF (non-IPF ILD) [16]. Moreover, an additional post hoc analysis of the study's results in the overall patient population that evaluated the predicted categorical absolute changes in FVC percentage (FVC%) over a 52-week study period showed that the percentage of patients experiencing clinically meaningful declines in FVC% (FVC decline _5%) was lower in the nintedanib group compared with that in the placebo group [107,108]. Currently, there are no data on the efficacy of nintedanib in patients with PF-ILDs beyond 52 weeks or data indicating the benefit of continuing antifibrotic treatment in patients with PF-ILDs who experience disease progression during such treatments. Data on the prognostic significance of FVC decline in the non-IPF ILD population are scarce. At the same time, studies in the IPF population have shown that FVC decline is a weak predictor of future FVC decline despite its association with mortality [109–111]. Published analyses of pooled data from registration trials for anti-fibrotic agents in IPF provided evidence that continued pirfenidone therapy benefited patients with IPF who had significant on-treatment disease progression (defined as a decline in FVC of _10% over 6 months of treatment), with a risk reduction with respect to further FVC decline or death [110]. A similar analysis of pooled data from the INPULSIS I and II studies suggested the benefit of continued treatment with nintedanib in patients with IPF despite disease progression [111].

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Recommendation 8:
We recommend that the same principles of non-pharmacological and palliative treatment and eligibility for lung transplantation should be applied in a patient with an interstitial lung disease other than IPF with progressive fibrosis as in a patient with IPF.

Evidence quality: very low
Strength of recommendation: strong
(voting results: strongly for—16 votes, conditionally for—10 votes, abstain from voting—3 votes, conditionally against—0 votes, strongly against—0 votes)

Commentary: *Taking into account the similarity of the natural history of PF-ILDs to that of IPF and the lack of alternative management options, the application of the same principles of non-pharmacological, palliative, and terminal care seems to be justified.*

Background
Non-pharmacological treatment of pulmonary diseases is a significant addition to pharmacological treatment regardless of diagnosis. Pulmonary rehabilitation is an important component of the support for the maintenance of function and quality of life of patients with IPF [112–115]. The number of randomized rehabilitation trials was low, and they included patients not only with IPF, but also with other ILDs,

including those associated with systemic autoimmune diseases, NSIP, sarcoidosis, and HP [116–121]. Patients with ILDs other than IPF benefit from rehabilitation irrespective of the degree of lung function impairment [122,123]. The improvement related to pulmonary rehabilitation was mainly associated with reduced dyspnea, prolonged walking distance, and improved quality of life [124]. Long-term home oxygen therapy is an established supportive therapy for respiratory failure in chronic obstructive pulmonary disease (COPD), and by analogy, it is also used in patients with respiratory failure due to other causes, e.g., ILDs. Exertional hypoxemia is commonly observed in ILD patients, and it necessitates the use of portable oxygen concentrators during exercise. There is no conclusive evidence for the efficacy of such treatment in improving exercise tolerance or survival. Two randomized studies confirmed a positive impact on the quality of life of patients with various ILDs who used portable oxygen concentrators during exercise, but these were studies in small groups of patients [125,126]. Palliative care is focused on reducing the symptoms of the disease and improving the quality of life of patients with chronic lung diseases. Given the symptoms that are common for IPF and other PF-ILDs, such as shortness of breath, cough, reduced exercise tolerance, and pain in some systemic autoimmune diseases, the indications and palliative therapy methods in these patients should not differ from those for IPF patients [127–129]. Lung transplantation is a treatment intended for patients with end-stage respiratory diseases with an expected graft-free survival of less than 2 years. The criteria for inclusion on the waiting list for patients with PF-ILDs do not differ from those used in IPF patients. Disease progression despite treatment and severe lung function impairment are the main indications [130].

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 06 of 12, June 2026) am 11.06.2026

#	Suchschritt
1	MeSH descriptor: [Pulmonary Fibrosis] explode all trees
2	((pulmonary OR lung) NEXT fibros*):ti,ab,kw
3	((progressive OR interstitial OR nonidiopathic OR idiopathic OR nonspecific OR "non-specific") AND (pulmon* OR lung* OR pneum*) AND (fibros* OR fibrot*)):ti,ab,kw
4	(alveoliti* AND (fibros* OR fibrot*)):ti,ab,kw
5	MeSH descriptor: [Lung Diseases, Interstitial] this term only
6	(interstitial NEXT (lung OR pneumon*)):ti,ab,kw
7	(diffuse AND parenchym* AND lung):ti,ab,kw
8	(IPF OR nonIPF OR PPF OR PFILD OR ILD OR NSIP OR SScILD OR RAILD OR SLEILD):ti,ab,kw
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	#9 with Cochrane Library publication date from Jun 2021 to present, in Cochrane Reviews
11	#10 with Cochrane Library publication date from Jun 2024 to present
12	#10 NOT #11

Leitlinien und systematische Reviews in PubMed am 11.06.2026

verwendete Suchfilter für Leitlinien:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 20.03.2026

verwendeter Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 01.01.2026.

#	Suchschritt
	Leitlinien
1	Pulmonary Fibrosis[mh]
2	pulmonary fibros*[tiab] OR lung fibros*[tiab]
3	(progressive[tiab] OR interstitial[tiab] OR nonidiopathic[tiab] OR idiopathic[tiab] OR nonspecific[tiab] OR non-specific[tiab]) AND (pulmon*[tiab] OR lung*[tiab] OR pneum*[tiab]) AND (fibros*[tiab] OR fibrot*[tiab])
4	alveoliti*[tiab] AND (fibros*[tiab] OR fibrot*[tiab])
5	Lung Diseases, Interstitial[mh:noexp]
6	interstitial lung[tiab] OR interstitial pneumon*[tiab]
7	diffuse[tiab] AND parenchym*[tiab] AND lung[tiab]

#	Suchschritt
8	IPF[tiab] OR nonIPF[tiab] OR PPF[tiab] OR PFILD[tiab] OR ILD[tiab] OR NSIP[tiab] OR SScILD[tiab] OR RAILD[tiab] OR SLEILD[tiab]
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(#9) AND (Guideline[pt] OR Practice Guideline[pt] OR Consensus Statement [pt] OR Consensus Development Conference, NIH[pt] OR guideline*[ti] OR recommendation*[ti] OR ((consensus[ti] OR position[ti]) AND (expert[ti] OR delphi[ti] OR statement*[ti] OR paper*[ti] OR document*[ti] OR report*[ti])))
11	(#10) AND ("2021/06/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews
13	(#9) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
14	(#13) AND ("2021/06/01"[PDAT] : "3000"[PDAT])
15	(#14) NOT "The Cochrane database of systematic reviews"[Journal]
16	(#15) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
17	#16 NOT #12
18	(#17) AND ("2024/06/01"[PDAT] : "3000"[PDAT])
19	#17 NOT #18

Iterative Handsuche nach grauer Literatur, abgeschlossen am 16.06.2026

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2026-B-130-z

Verfasser	
Name der Institution	Deutsche Gesellschaft für Pneumologie
Datum der Erstellung	23.06.2026

Indikation
Behandlung von Erwachsenen mit progredienter pulmonaler Fibrose (PPF).
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Patienten mit interstitiellen Lungenerkrankungen, die nicht einer idiopathischen pulmonalen Fibrose (IPF) entsprechen, können mit unterschiedlicher Häufigkeit einen progredient-fibrotischen Verlauf nehmen, der durch eine Zunahme der Atembeschwerden, eine Abnahme des Lungenvolumens (gemessen als forcierte Vitalkapazität, FVC) und/oder der Diffusionskapazität und/oder die eine Zunahme der fibrotischen Veränderungen in der hochauflösenden Computertomographie gekennzeichnet ist (1,2). Die entsprechenden internationalen und Deutschen Leitlinien geben hierfür Kriterien vor, die nach Ausschluss anderer Ursachen wie interkurrente Infekte, Herzinsuffizienz, Lungenembolie etc. eine zunehmende Fibrosierung des Lungengewebes anzeigen und dann eine antifibrotische Therapie erfordern (1,2). Zugelassen hierfür ist das Antifibrotikum Nintedanib, ein Tyrosinkinase-Inhibitor, basierend auf der INBUILD-Studie (3). Wahrscheinlich ebenfalls wirksam ist auf Basis der RELIEF-Studie Pirfenidon, allerdings musste die RELIEF-Studie aufgrund zu langsamer Rekrutierung vorzeitig abgebrochen werden, ist daher nur bedingt aussagekräftig und führte nicht zur Zulassung von Pirfenidon in dieser Indikation (4). Auf Basis dieser Studien ist Nintedanib in Deutschland zur Therapie der progredienten pulmonalen Fibrose (PPF) zugelassen, während dies für Pirfenidon nicht der Fall ist. Die Deutsche S2k Leitlinie empfiehlt dem entsprechend bei Diagnosestellung einer progredienten pulmonalen Fibrose die Einleitung einer antifibrotischen Therapie mit Nintedanib als Erstlinioentherapie, bei Unverträglichkeit oder nicht Wirksamkeit von Nintedanib wird jedoch auch der off-lable use von Pirfenidon empfohlen und als gerechtfertigt beurteilt (1). Bezüglich der Wirksamkeit von Nintedanib bei Patienten mit PPF ist ein verminderter Abfall der forcierten Vitalkapazität im zeitlichen Verlauf gesichert, sodass eine Verzögerung der Krankheitsprogression erreicht werden kann. Die sekundären Endpunkte der Studie einschließlich Lebensqualität im K-BILD Fragebogen, akute Exazerbation und Mortalität, numerisch zu Gunsten der Therapie mit Nintedanib verschoben, erreichten jedoch keine statistische Signifikanz (3). Die Problematik der Nebenwirkungen von Nintedanib insbesondere gastrointestinale Beschwerden und Diarrhöen besteht bei Patienten mit PPF in gleicher Weise wie im Statement zu IPF dargestellt (5). Auch hier erfolgt die Therapie unter Abwägung des begrenzten

therapeutischen Nutzens und der möglichen Nebenwirkungen, was bei vielen Ärzten zu einer eher zurückhaltenden Verschreibungspraxis führt.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Im Gegensatz zu der idiopathischen Lungenfibrose besteht bei vielen interstitiellen Lungenerkrankungen die Indikation für eine immunsuppressive Therapie mit Prednisolon und ggf. in Kombination mit Immunmodulatoren wie Azathioprin, Mycophenolat Mofetil oder auch Rituximab, letzteres insbesondere, wenn eine rheumatische Grunderkrankung bzw. eine Kollagenose vorliegt (1). Die Indikationsstellung, ab wann eine immunmodulatorische Therapie nicht mehr zielführend und eine antifibrotische Therapie begonnen werden sollte muss im Einzelfall anhand der klinischen, funktionellen, immunologischen und radiologischen, ggf. zytologischen (BAL) oder histologischen Befunden und im zeitlichen Verlauf festgelegt werden (6). Unter bestimmten Bedingungen muss jedoch auch in Betracht gezogen werden, dass eine immunmodulatorische oder immunsuppressive Therapie negative Konsequenzen für den Patienten hat, dies ist insbesondere dann zu berücksichtigen, wenn in der hochauflösenden Computertomographie ein typisches UIP-Muster (Usual Intersitial Pneumonia) vorliegt, welches einen definitiven fibrotischen Umbau des Lungengewebes anzeigt. Dies gilt insbesondere für PPF Patienten mit verkürzten Telomeren, bei denen sich eine immunsuppressive Therapie negativ auswirken kann, unabhängig davon ob eine Mutation im Telomerasekomplex nachgewiesen werden kann oder nicht (7-9). Da die Bestimmung der Telomerlänge derzeit nicht als klinisches Standardverfahren durchgeführt werden kann müssen klinische Indikatoren herangezogen werden, die auf verkürzte Telomere hinweisen zum Beispiel ein frühes Ergrauen der Haare, oder auch hämatologische Auffälligkeiten wie zum Beispiel Anämie, Leukozytopenie oder Thrombozytopenie, die auch gering ausgeprägt sein können (10). Dementsprechend sollten Patienten mit progredienter pulmonaler Fibrose insbesondere bei Vorliegen eines UIP-Musters im HRCT und bei klinischen Hinweisen auf ein „short telomer syndrome“ oder generell auf verkürzte Telomere aufweisen eine immunmodulatorische Therapie unterlassen und eine alleinige antifibrotische Therapie durchgeführt werden. In vielen Fällen wird auch eine Kombination aus immunmodulierender und antifibrotische Therapie erforderlich sein, insbesondere dann, wenn eine rheumatische Erkrankung oder eine Kollagenose zugrunde liegt, wie eine extrapulmonale Manifestation die eine immunmodulatorische Therapie erfordern (1). In entsprechenden ILD-Zentren ist eine enge Kooperation zwischen Pneumologen und Rheumatologen inzwischen vielerorts etabliert, um dieser Notwendigkeit gerecht zu werden.

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