Add-on therapy for pulmonary fibrosis, a forthcoming era with implications for practice: the BI 101550 and RELIEF trials

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Antifibrotic medication is increasingly complex. Add-on treatments are in clinical trials, or available, for patients progressing on first-line IPF or PFILD therapy. We review the BI 101550 and RELIEF trials, placing them within current clinical practice. https://bit.ly/3oYSKKd

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Abstract

The therapeutic landscape for idiopathic pulmonary fibrosis (IPF) and progressive fibrosing interstitial lung disease (PFILD) is increasingly complex, with add-on antifibrotic options now in clinical trials, or available for patients progressing on first-line therapy in both conditions. Here, we review two recent trials of potential add-on therapeutic options, the BI 101550 and RELIEF trials. BI 101550 was a phase 2 randomised control trial (RCT) of a novel phosphodiesterase-4 inhibitor in patients with IPF, with a primary end-point of change in forced vital capacity (ΔFVC) (in mL) at 12 weeks. The RELIEF trial was a phase 2 RCT in patients with PFILD, with a primary end-point of ΔFVC (absolute % predicted) over 48 weeks. Whilst the BI 101550 and RELIEF trials showed positive results in their primary end-points, the strengths and weaknesses of both trials are discussed with importance for their interpretation and clinical impact. We review current clinical practice in IPF and PFILD and place the BI101550 and RELIEF trial results in context, highlighting advances and problems with antifibrotic therapies.

Commentary on:

- Richeldi L, *et al.* Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. N Engl J Med 2022; 386: 2178–2187.
- Behr J, *et al.* Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med 2021; 9: 476–486.

Context

Fibrosing interstitial lung disease (FILD) forms a subgroup of interstitial lung disease (ILD) and is characterised by the accumulation of excessive extracellular matrix, with destruction of normal lung architecture [1, 2]. FILDs include: idiopathic pulmonary fibrosis (IPF); idiopathic nonspecific interstitial pneumonias (NSIP); other idiopathic interstitial pneumonias; connective tissue disease associated autoimmune ILDs (CTD-ILD); other autoimmune ILDs; fibrosing hypersensitivity pneumonitis; other exposure-related ILDs (*e.g.* asbestosis, silicosis); Langerhans cell histiocytosis; and unclassifiable idiopathic interstitial pneumonias [1, 3]. Whilst the clinical course of the FILDs can vary, a proportion of patients with each condition are at risk of developing a progressive fibrosing phenotype [4]. This progressive fibrosing ILD (PFILD) phenotype is characterised by ongoing extracellular matrix deposition resulting in physiological, radiological, and functional decline [3, 5, 6]. The description of PFILD mirrors the natural history of IPF, considered the archetypal PFILD due to the inevitability of progression [1]. This

has led to an interest in utilising pirfenidone and nintedanib, approved antifibrotic therapies shown to be effective in slowing the decline of lung function in IPF, in PFILD [7, 8]. The term PFILD usually describes non-IPF PFILD, as it shall here.

Pirfenidone was shown to have antifibrotic properties in preclinical studies as early as 1994, entering clinical practice for IPF in Japan in 2008, followed by Europe in 2011 [9]. Evidence for clinical benefit from pirfenidone was based upon initial randomised control trials (RCTs) conducted in Japan, and the subsequent CAPACITY and ASCEND trials [10–13]. The mechanism of action of pirfenidone is still incompletely understood, especially as a small hydrophobic molecule it doesn't require a receptor to gain cell entry [14]. Pirfenidone is a synthetic molecular derivative of pyridine and has been shown to regulate profibrotic signalling pathways, including TGF-β (transforming growth factor-β), PDGF (platelet-derived growth factor) and b-FGF (basic fibroblast growth factor) [15–18]. Further, it modulates regulators of collagen and extracellular matrix such as matrix metalloproteinases and tissue inhibitors of metalloproteinases [19–21]. Pirfenidone may also have effects upon a wide range of immune cells and pro-inflammatory cytokines [14, 22, 23].

Nintedanib was the second antifibrotic medication to enter clinical practice, being authorised in Europe and North America in 2015 based on the INPULSIS and TOMORROW trials [24–26]. Nintedanib is a small molecule inhibitor of several tyrosine kinase receptors: PDGF receptor, fibroblast growth factor receptor and vascular endothelial growth factor (VEGF) receptor [27, 28]. Further, nintedanib inhibits the TGF-β receptor and non-receptor tyrosine kinases [28]. These receptors facilitate downstream intracellular signalling from important profibrotic signalling cytokines including PDGF, VEGF and TGF-β, with nintedanib receptor blockade of their receptors reducing extracellular matrix protein secretion by cells [27, 29]. Additionally, inhibition of non-receptor kinases is important to T- and B-cell function and haematopoiesis [28, 30].

There has been no definitive PFILD criteria to guide trial inclusion criteria, and the concept is not without controversy, with incomplete understanding and research of the pathobiology of this phenotype [2, 31]. To address this the 2022 American Thoracic Society (ATS)/European Respiratory Society (ERS) IPF and progressive pulmonary fibrosis (PPF) guideline attempts to standardise diagnosis and renames PFILD "progressive pulmonary fibrosis (PPF)" [3, 8]. The PPF guidelines acknowledge low-grade evidence, and made a number of research recommendations due to insufficient evidence [3]. Further, the INBUILD RCT forms the basis of the ATS/ERS guideline committee treatment recommendation of nintedanib therapy for PFILD patients; however, the PPF diagnostic criteria are divergent from the INBUILD PFILD inclusion criteria (table 1) [3, 8]. Pirfenidone has also been investigated in a number of trials for the progressive phenotype in specific FILDs, with trials summarised in table 2. The recent RELIEF trial of pirfenidone in PFILD, reviewed here, is the intended counterpart to the INBUILD trial [7, 8].

Nintedanib is often an add-on therapy in patients with PFILD, with many patients receiving immunosuppression as first line. Patients with IPF currently do not have add-on therapeutic options, with ATS/ERS guidelines recommending either pirfenidone or nintedanib. Head-to-head trials are lacking, with choice usually guided by patient comorbidities or preferences based upon potential side-effects. Whilst small phase IV studies have assessed the safety of nintedanib as add-on therapy to pirfenidone, and pirfenidone as add-on therapy to nintedanib, results from the PROGRESSION RCT (ClinicalTrials.gov identifier: NCT03939520) comparing the efficacy of switching monotherapy to add-on therapy in disease

TABLE 1 Comparison of the diagnostic criteria for progressive pulmonary fibrosis (PPF) in the ATS/ERS 2022 idiopathic pulmonary fibrosis and PPF guideline update and the INBUILD progressive fibrosing interstitial lung disease (PFILD) randomised control trial inclusion criteria

	ERS/ATS PPF criteria [3] (any 2 criteria)	INBUILD trial PFILD criteria [8]
Forced vital capacity	Absolute decline ⩾5%	Relative decline >10% OR 5–10% and any of the below criteria
Symptoms	Worsened respiratory symptoms	Worsened respiratory symptoms
D_{LCO}	Absolute decline ⩾10%	Not included
Radiology	Worsened fibrosis on HRCT	Worsened fibrosis on HRCT
Time-period decline/investigations must be within	12 months	24 months

ATS: American Thoracic Society; ERS: European Respiratory Society; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography.

TABLE 2 Summary of pirfenidone and nintedanib trials conducted in progressive fibrosing interstitial lung diseases (PFILDs)

PFILD (non-IPF)	Trial	Nintedanib/ pirfenidone
PFILD (CTD-ILD; fHP; autoimmune lung fibrosis; NSIP; unclassifiable IIP; sarcoidosis; others)	INBUILD [8]	Nintedanib
PFILD (CTD-ILD; NSIP; fHP; asbestosis)	RELIEF [7]	Pirfenidone
Sarcoidosis PFILD	PirFS [32]	Pirfenidone
Unclassifiable PFILD	Pirfenidone in unclassifiable PF-ILD [33]	Pirfenidone
Pneumoconiosis PFILD	NiPPS (ClinicalTrials.gov identifier: NCT04161014, expected completion 2025)	Pirfenidone
Pulmonary fibrosis with anti- myeloperoxidase antibodies PFILD	PIRFENIVAS [34]	Pirfenidone

IPF: idiopathic pulmonary fibrosis; CTD-ILD: connective tissue disease associated ILD; NSIP: nonspecific interstitial pneumonia; fHP: fibrosing hypersensitivity pneumonitis; IIP: idiopathic interstitial pneumonia; INBUILD: Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease; RELIEF: Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis; PirFS: Pirfenidone for Progressive Fibrotic Sarcoidosis; NiPPS: The Nintedanib in Progressive Pneumoconiosis Study; PIRFENIVAS: Pilot Study of Pirfenidone in Pulmonary Fibrosis with Anti-myeloperoxidase Antibodies. Notable fibrosing ILD trials, excluded due to lack of progression in inclusion criteria, include the TRAIL 1 (Pirfenidone in rheumatoid arthritis associated ILD) and SENSCIS trials (Nintedanib in systemic sclerosis associated ILD) [35, 36].

progression are awaited [37, 38]. Here, we review a phase 2 RCT of the efficacy of a novel phosphodiesterase-4 (PDE4) inhibitor as add-on therapy to standard of care treatment, namely antifibrotic treatment with nintedanib or pirfenidone or no background antifibrotic treatment [39].

Methods: BI 1015550

BI 1015550 is a PDE4 inhibitor with preferential enzymatic inhibition of PDE4B, that showed antifibrotic and anti-inflammatory properties [39, 40]. This phase 2 trial was conducted at 90 sites in 22 countries, and 147 patients. Inclusion criteria were: age 40 years or older; diagnosis of IPF; definitive or probable usual interstitial pneumonia high-resolution computed tomography radiological pattern; forced vital capacity (FVC) at least 45% predicted; diffusing capacity of the lung for carbon monoxide (D_{LCO}) 25–80% predicted. Participants were eligible if treatment naïve, or if taking a stable dose of pirfenidone or nintedanib for 8 weeks or more. Allocation of participants was random in a 2:1 ratio to receive either BI 1015550 (18 mg) or placebo twice daily.

The primary end-point was FVC change at 12 weeks. The secondary end-point was the percentage of patients with treatment-emergent adverse events (TEAEs). Further objectives, whose results are only partially published, were 1) to assess further efficacy based on the quality-of-life questionnaires and additional lung function assessments; 2) to explore the pharmacokinetics of BI 1015550 in IPF patients with or without antifibrotic treatment; 3) to assess exploratory IPF biomarkers, specific blood protein markers, and unspecified mRNAs, miRNAs and metabolite markers from whole blood or plasma, respectively.

End-points were evaluated separately according to background non-use or use of an antifibrotic agent at baseline. The analysis was conducted first with a restricted maximum likelihood-based approach using a mixed model with repeated measures (MMRM). Secondly, with a Bayesian approach, where the adjusted means in the placebo groups were combined with the meta-analytic predictive (MAP) priors, which were derived based on prior clinical trials for nintedanib. In MMRM missing data for the primary analysis were not imputed, under the assumption that they are missing at random. Sensitivity analyses were successively run to assess the potential effect of missing data and early discontinuation.

Results: BI 1015550

132 patients (90%) completed the planned treatment period. A total of 15 patients prematurely discontinued BI 1015550, and no patients discontinued the placebo. Adverse events were the primary reason for premature discontinuation, with diarrhoea as the most common side-effect. The change in the FVC favoured the treatment over the placebo in both groups: patients with background use of antifibrotic drugs and those without. In the latter group, the stabilisation of lung function in the treatment group was observed. Results were confirmed in both MMRM, and a Bayesian analysis. In MMRM, the mean between-group difference in the FVC was 101.7 mL (95% CI 25.0–178.4 mL) among patients without background antifibrotic use and 80.4 mL (95% CI 20.9–140.0 mL) among patients with background antifibrotic use. In the Bayesian analysis, the posterior median between-group difference in the FVC was 88.4 mL (95% credible interval 29.5–154.2 mL) among patients without background antifibrotic use and

62.4 mL (95% credible interval 6.3–125.5 mL) among patients with background antifibrotic use. The change in the percentage of the predicted value for D_{LCO} was similar in the two groups; with an adjusted mean difference of 0.8 percentage points (95% CI −3.5–5.0) at 12 weeks among patients without background antifibrotic use. Among patients with background antifibrotic use, the adjusted mean difference between the trial groups was 2.8 percentage points (95% CI −0.4–5.9). The adjusted mean changes in the Living with Pulmonary Fibrosis questionnaire total score from baseline to week 12 were similar across the trial groups, regardless of background treatment.

Methods: RELIEF

The RELIEF trial was a phase 2b, multicentre, double-blind, randomised, placebo-controlled study conducted in 17 ILD centres in Germany [7]. Eligible patients were adults (18–80 years) with a progressive fibrotic phenotype (PFILD) secondary to four diagnoses: CTD-ILD, fibrotic NSIP, chronic hypersensitivity pneumonitis, or asbestos-induced lung fibrosis [7]. Further inclusion criteria were FVC 40–90% predicted and a D_{LCO} 25–75% predicted at baseline in addition to disease progression, defined as annual FVC decline >5% predicted despite conventional therapy, over 6–24 months before enrolment. Patients with previous antifibrotic treatment were excluded, prior immunosuppression was permitted. Participants were randomly assigned in a 1:1 ratio to receive pirfenidone or placebo in addition to their ongoing medication for 48 weeks, followed by an open label extension period. The primary end-point was the absolute change in the percentage of predicted FVC over the 48-week period. This efficacy end-point was analysed in the intention-to-treat population, conducting an additional per-protocol analysis for the *post hoc* sensitivity analysis. Secondary end-points were progression-free survival; categorical assessment of relative changes in predicted FVC of <5%, 5% to <10%, and ⩾10%; D_{LCO}; exercise capacity (6-min walking distance); quality of life (St George's respiratory questionnaire); time to clinical deterioration; and safety (adverse and serious adverse event frequency). Despite a protocol amendment extending D_{LCO} criteria to 10–90% predicted due to low recruitment, an early interim analysis was requested by the data monitoring committee. It resulted in the early termination of the trial because of futility, all patients were withdrawn from the study drug.

Results: RELIEF

In the RELIEF trial 142 patients were screened, of which 127 were randomly assigned to pirfenidone (n=64) or placebo (n=63) [7]. The study was terminated early by the ethics committee because of futility, after 34% of the intended total sample size had been enrolled. At study termination outcome data on the primary end-point was missing in 29 participants (23%), a further 31 participants (24%) were excluded for other reasons as per the study protocol. As a result, data for 60 (47%) patients needed to be imputed using the sum of squared differences (SSD) imputation method for missing data, in which deceased patients were assigned the worst rank. Within this framework, in the intention-to-treat population (n=127), rank ANCOVA showed significantly reduced FVC decline (% predicted; p=0.043) in patients treated with pirfenidone compared with placebo. Findings were similar when the model was stratified by diagnostic group (p=0.042). The estimated median difference between pirfenidone and placebo groups for the primary end-point was 1.69 FVC % predicted (95% CI −0.65–4.03). To assess robustness of data several *post hoc* sensitivity analyses were performed, applying the last observation carried forward analysis (LOCF) and multiple imputation methods; they consistently found a reduction in FVC decline within the pirfenidone group (p=0.042 for LOCF; p=0.041 for multiple imputation). Additional ascertainment was also conducted through a per-protocol analysis with unimputed raw data. The sensitivity analyses performed in the per-protocol population encompassed 46 patients in the pirfenidone group and 50 in the placebo group, who strictly adhered to the study protocol without serious adverse events. Those per-protocol analyses of the primary outcome undertaken without data imputation were all nonsignificant (p=0.092 for rank ANCOVA-based analysis of the entire per-protocol population; p=0.065 for the model stratified by diagnostic group). The analyses of secondary outcomes were also nonsignificant, except for D_{LCO}. No safety concerns and new or unexpected adverse events arose from the addition of pirfenidone to the underlying immunosuppressive therapy.

Commentary

The BI 1015550 trial indicates the molecule is promising in preserving lung function [39]. The main limitation is study length, at only 12 weeks. Whilst a recent meta-analysis showed that 3- month declines in lung function are highly predictive of 12-month change, this interval may be insufficient to thoroughly assess the safety of the drug [41]. In this specific case, BI 1015550 showed an increased risk of vasculitis in preclinical studies [40]. A case of suspected vasculitis and IPF exacerbation happened in one patient with background antifibrotic use, although the vasculitis was not confirmed by an independent data monitoring committee.

The statistical plan incorporating Bayesian statistics is notable. This approach is based on Bayes' theorem, which describes the probability of an event occurrence, based on previous knowledge of the conditions associated with this event. The validity is maintained as long as the prior probability model is correctly specified, and the priors correctly sampled. The main objection to Bayes' theorem is that a prior is subjective, and secondly there is no single, well-defined method for choosing a prior. This can lead to the selection of different priors for the same experiment and thus obtain different posteriors and make different conclusions [42]. Bayes' theorem has been extensively explained elsewhere [43, 44]. In the BI 1015550 trial priors were chosen to reflect an effective sample size based on historical patients who had received placebo in nintedanib registration trials. This allowed use of an unbalanced ratio (2:1) for participant allocation, favouring the treatment arm. In the context of rare diseases, such as IPF, where recruitment is challenging given the low prevalence of the disease, Bayes' theorem represents a valuable tool to ensure the validity of conclusions, even with smaller study populations.

The BI 1015550 trial is important, as it places the trial drug within routine clinical practice as an add-on therapy and clearly shows great promise in this role. Optimism should be tempered until phase 3 trials confirm therapeutic benefit. Historically, it has proven difficult for phase 2 compounds to progress through phase 3 trials as shown by ziritaxestat, the most recent example [45]. The progress from having no licensed, effective, antifibrotic therapies to add-on therapies is impressive. However, so is the multidisciplinary expertise and pharmacovigilance required to maintain safe and effective care with increasingly complex therapeutics. Real world data will be even more crucial moving forward into the era of dual antifibrotic therapy.

The RELIEF trial aimed to investigate the efficacy and safety of pirfenidone in four well characterised ILD entities with a progressive fibrotic phenotype [7]. Although pirfenidone was previously tested for progressive unclassifiable ILD, the RELIEF study is the only RCT investigating pirfenidone in progressive fibrosing (non-IPF) ILD, in addition to conventional therapy [7, 33]. A significant reduction in the primary end-point (absolute ΔFVC % predicted) was reported for patients treated with pirfenidone according to pre-specified analysis and imputation rules. Additionally, a similar safety and tolerability profile was shown for pirfenidone to that described for previous IPF trials, despite concurrent immunomodulatory therapy. However, these results need to be interpreted cautiously in the context of the limitations of the study. Data were missing in 60 (47%) out of 127 enrolled patients, which might have contributed to study findings. The early termination of the trial resulted in a substantial sample size reduction from the initial study design, alongside high numbers of missing values. In this setting, sensitivity analysis of the primary end-point and analysis of secondary outcomes undertaken without imputation were found to be nonsignificant, except for D_{LCO}. Data exclusion from deceased patients derived a loss of significance for all tested models regardless of the imputation method, suggesting the uneven distribution of deaths between study groups (n=5 in the placebo group, n=1 in the pirfenidone group) might partly explain the significant treatment effect of the imputed analyses. In this scenario, results from the RELIEF trial showed a safe and tolerable side-effect profile for pirfenidone treatment in addition to ongoing immunosuppressive therapy, with a possible attenuation of functional disease progression in PFILD patients.

The prior lack of standardised criteria for progression in FILD means that meta-analysis of RCT data is problematic, hampering the ability to combine the multiple RCTs in FILD diseases and therefore increase power or draw conclusions across a wider range of FILDs. This would be especially useful for pirfenidone, given the multiple trials across different PFILDs (table 2) [7, 32, 33, 35]. Parallel lack of standardisation of clinical practice guidelines and trial criteria (table 1) is explained by the fact guidelines were informed by limited evidence, largely derived from these separate trials [3, 31]. This creates additional complexity for clinicians, where subgroups of patients that they diagnose with PFILD (PPF) may not be eligible for the treatment recommended by the guideline, with authorisation (whether insurer, regulatory or governmental) decisions made based upon the informative clinical trial(s) [3].

Clinicians are now left with uncertainty with regards to the role of pirfenidone in PFILD. The RELIEF trial offers limited evidence that pirfenidone may be effective in ameliorating progression of FILD [7]. Whether this is strong enough for clinicians to consider its use in clinical practice is difficult, with patients who are intolerant, progress, or in whom nintedanib is contraindicated currently without other treatment options. Furthermore, from a global perspective there is inequality of access to antifibrotic medications, with nintedanib still under patent. Pirfenidone is now available in generic formulations, increasing its accessibility in many regions, making the question of pirfenidone efficacy in PFILD of even greater importance.

The BI 1015550 and RELIEF trials highlight the importance of clinical trial design [7, 39]. The RELIEF trial was ended due to futility, in large part driven by relatively restrictive inclusion criteria (FVC decline >5% based on three spirometry readings) and thus reduced statistical power [7]. Whilst the BI 1015550

trial shows the difference alternate (Bayesian) methodology can have to ensuring the validity of findings, another revolutionary approach in clinical trials design is approaching ILD trials, with the use of the Randomised Embedded Multifactorial Adaptive Platform (REMAP) [46]. This has been tested initially for defining efficacy of treatments for community-acquired pneumonia, and, more recently, for coronavirus disease 2019 [46, 47]. A global project for ILD is planned [48].

Implications for practice

Currently nintedanib or pirfenidone are recommended treatments for IPF, with contraindications and side-effect profile largely governing patient selection. There are currently no head-to-head clinical trials to

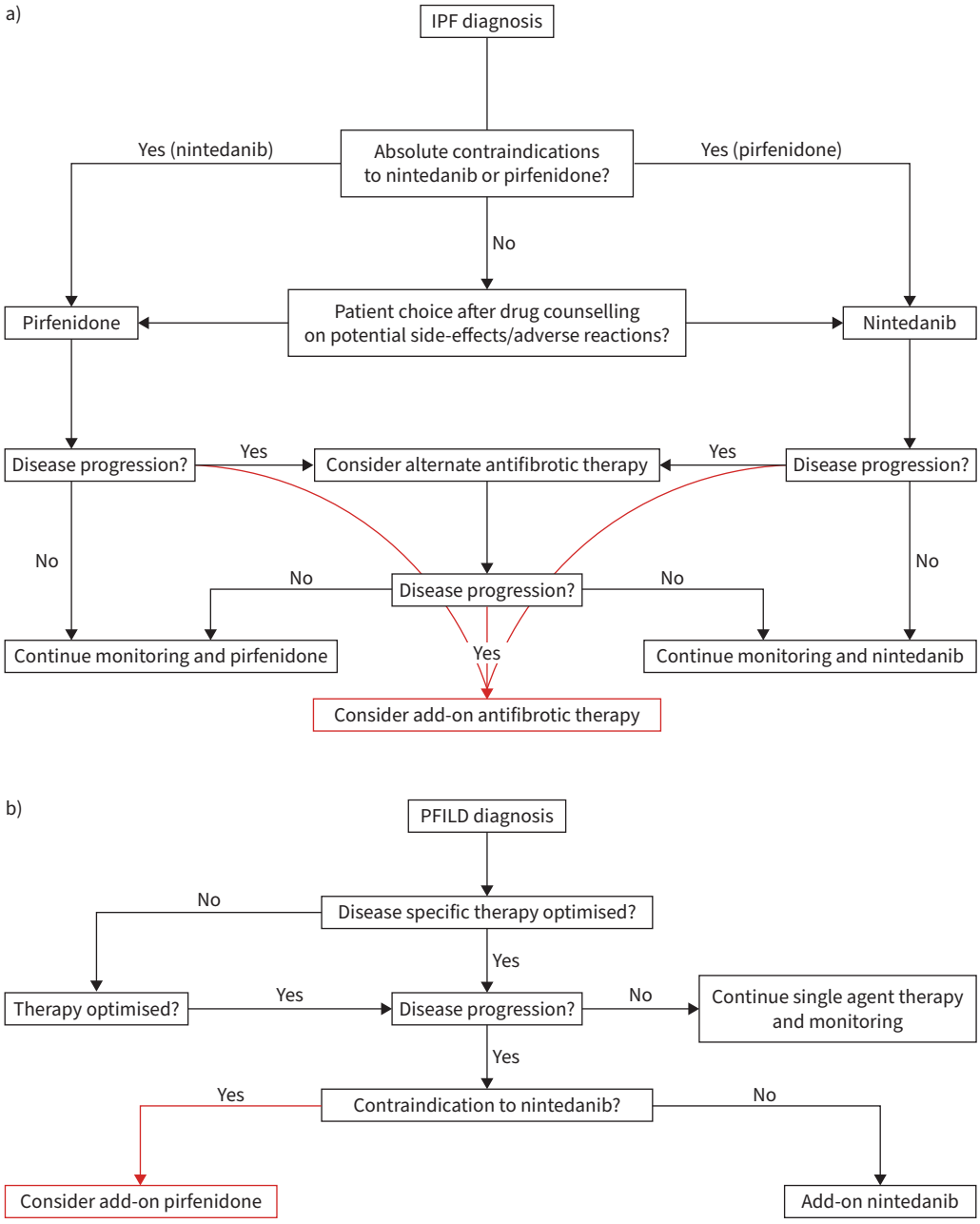

FIGURE 1 a) shows idiopathic pulmonary fibrosis (IPF) and b) progressive fibrosing interstitial lung disease (PFILD) antifibrotic treatment algorithms. Other therapies are not shown. Black boxes show current treatments and pathways, red boxes and arrows show possible future treatments and pathways based upon the BI 1015550 and RELIEF trials [3, 7, 8, 39].

guide drug selection based upon efficacy. If patients either progress, or become intolerant, of their medication it is reasonable to consider changing to the alternate antifibrotic [49, 50]. The BI 1015550 trial shows add-on antifibrotic therapies entering clinical practice is a likelihood in the near medium-term future, with a phase 3 trial of BI 101550 (ClinicalTrials.gov identifier: NCT05321069) in progress. Antifibrotic treatment in IPF is summarised in figure 1a.

Nintedanib is currently recommended for PFILD (PPF) patients who have disease progression despite optimal first-line therapy (*e.g.* immunosuppression for CTD-ILD). There is no current recommendation for pirfenidone treatment in PFILD, with limited evidence from the RELIEF trial suggesting it may be effective with a similar rate of adverse events as in IPF. Whether pirfenidone should be considered in treating patients who are unsuitable for, or unable to access, nintedanib is currently unclear. Antifibrotic treatment in PFILD is summarised in figure 1b.

Patients with PFILD and IPF often have multiple comorbidities and polypharmacy. Consequently, antifibrotic medication management requires specialist multidisciplinary team input including pharmacists, physicians and specialist nurses. As add-on therapies become available the complexity of antifibrotic prescribing and necessity of specialist multidisciplinary teams will increase further.

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