Drugs Aging (2017) 34:647–653
DOI 10.1007/s40266-017-0488-0

LEADING ARTICLE

Managing Idiopathic Pulmonary Fibrosis: Which Drug for Which Patient?

Conal Hayton[1] · **Nazia Chaudhuri**[2]

Published online: 31 August 2017

Abstract Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease with high mortality. Two novel antifibrotic agents, pirfenidone and nintedanib, have received licences for use in IPF in recent years. Phase III, multinational, randomised control trials have provided evidence that both drugs reduce decline in forced vital capacity (FVC) over time, while further post hoc studies have suggested that both pirfenidone and nintedanib can be efficacious, regardless of age and severity of baseline lung function. Both therapeutic agents have manageable side effect profiles. In the absence of head-to-head data, decisions regarding which agent to choose when starting treatment for IPF should take into consideration joint decision making between patients and clinicians based on accurate information in the decision-making process. Questions remain as to the role of combination antifibrotic therapy as a future treatment option.

Key Points

New evidence from post hoc studies from key clinical trials in idiopathic pulmonary fibrosis (IPF) has reinforced the potential benefits of antifibrotic therapy.

Therapeutic trials in IPF have some limitations but in general are representative of the patient population.

Both antifibrotic treatments have side effect profiles that can be successfully managed through patient and physician education and joint decision making.

1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung condition that predominantly effects the elderly population. It is associated with significant morbidity and mortality, with a median survival of 3–5 years [1]. Over the last 5 years, the therapeutic management of IPF has undergone a major transformation. Evidence-based treatment options were disappointing until the arrival of two promising novel antifibrotic agents, pirfenidone and nintedanib. These disease-modifying agents have been recognised by international guidelines as first-line treatment for IPF [2] and provide the patient and physician with a welcome choice of treatment to slow disease progression. In this review, we will discuss recent post hoc data from leading clinical trials and examine how this can be used to guide management in clinical practice.

✉ Conal Hayton
conalhayton@doctors.org.uk

[1] Respiratory Medicine, North Manchester General Hospital, Manchester, UK

[2] North West Interstitial Lung Disease Unit, University Hospital of South Manchester, Manchester, UK

2 Pirfenidone and Nintedanib: The Original Data

2.1 Pirfenidone

Pirfenidone is an immunosuppressant with anti-inflammatory and antifibrotic properties developed for use in IPF [3]. Its mechanism of action is not fully understood. Following positive results from two double-blind, placebo-controlled trials in Japan [4, 5], the *Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes* (CAPACITY) trial programme was completed in 2011 to provide more robust evidence for the efficacy of pirfenidone [6]. This comprised two concurrent, multinational, randomised control trials (PIPF-004 and PIPF-006) comparing pirfenidone with placebo over a 72-week period. The primary endpoint was achieved in PIPF-004, with a significant reduction in the decline in forced vital capacity (FVC) in the 2403 mg/day pirfenidone group; however, this was not mirrored in PIPF-006. Nonetheless, a prespecified analysis of the pooled population of both trials found a significant benefit from pirfenidone, with a decline in percentage predicted FVC of 8.5 versus 11% for placebo. There was also a reduction in the number of patients experiencing a decline in FVC of $\geq$10% predicted, a marker of disease progression, at 72 weeks. Pirfenidone did not convey a symptomatic or mortality benefit, although the study was not powered to investigate the latter.

Due to discrepancies between the two trials in meeting its primary endpoint, the US FDA requested a further multinational, phase III, double-blind, randomised control trial, the *Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis* (ASCEND) study, which was published in 2014 [7]. In this study, 278 patients received pirfenidone (2403 mg/day) and 277 received placebo for 52 weeks. The primary endpoint was progression of disease at 52 weeks, defined as an absolute decline in percentage predicted FVC of $\geq$10%, or death. This was achieved with a 47.9% reduction in the number of patients experiencing progression of disease. Again, there was no improvement in dyspnoea or mortality. Following the publication of the ASCEND trial, in October 2014 pirfenidone received approval from the US FDA for use in IPF, having received full European Medicines Agency (EMA) approval by 2013 and National Institute for Health and Care Excellence (NICE) approval in April 2014.

2.2 Nintedanib

Nintedanib is a tyrosine kinase inhibitor licenced for use in non-small cell lung cancer and IPF. Its mechanism of action is through inhibition of platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β, leading to suppression of fibrosis [8]. The INPULSIS trials published in 2014 were designed to test the efficacy of nintedanib as a disease-modifying agent in IPF [9]. INPULSIS 1 and 2 were identical phase III, double-blind, randomised, placebo-controlled trials involving patients from 24 countries around the world. A total of 638 patients were randomised to receive nintedanib and 423 were randomised to receive placebo for 52 weeks. The treatment group achieved the primary endpoint, with a reduction in the rate of decline in absolute FVC at 12 months. Significant reductions were also seen in the proportion of patients who responded to treatment (defined as a change in percentage predicted FVC of $\leq$5 or $\leq$10% from baseline). There was no significant improvement in symptom scores or mortality. Following the publication of the INPULSIS trials, nintedanib received US FDA and EMA approval in 2014, and NICE approval in the UK in early 2016.

3 Pirfenidone and Nintedanib: Post Hoc Studies

Since the publication of these pivotal clinical trials, there have been multiple publications presenting post hoc analysis of the key trials in antifibrotic therapy to further reinforce the potential benefits of treatment. Post hoc analyses have their statistical limitations, however they can provide important insight on the benefits of antifibrotic treatment.

3.1 Pirfenidone

An FDA-requested, prespecified, pooled analysis of the combined data from the CAPACITY and ASCEND studies aimed to strengthen the evidence for the beneficial effects of pirfenidone [10]. It showed that at 1 year, pirfenidone significantly reduced the number of patients who had a $\geq$10% decline in predicted FVC or death, and increased the number of patients who had no decline by 59.3%. Another FDA-requested, prespecified, combined analysis demonstrated that pirfenidone significantly reduced the risk of all-cause and IPF-related mortality at 52 weeks [11]. The influence of baseline disease severity on efficacy was assessed in a study that split the combined data group based on percentage predicted FVC [12]. Patients were split into percent predicted FVC $\geq$80%, indicating 'milder' disease, and $\leq$80%, suggesting more 'severe' disease. In this post hoc analysis, pirfenidone significantly reduced the proportion of patients having a $\geq$10% decline in FVC or death in both disease groups, with no difference between the two. This analysis strengthens the efficacy of pirfenidone in a cohort of patients incorrectly depicted as 'milder' in their

phenotype because of an FVC >80% predicted. The British Thoracic Society (BTS) registry data demonstrate that patients with an FVC >80% predicted are significantly symptomatic, seek healthcare input, and have a mean diffusion capacity of the lungs for carbon monoxide (DLCO) of 48%, depicting significant disease burden [13]. This directly challenges the UK NICE decision to restrict pirfenidone use to patients with an FVC of 50–80% predicted [14]. This is a complex cost-effective analysis, not a clinical effectiveness decision, and this post hoc analysis lends important weight to the finding that patients benefit from antifibrotic therapy early in their disease when FVC is often >80% predicted. NICE also mandate that patients should have treatment discontinued if there is a decline in FVC of ≥10% predicted in 12 months, denoting treatment failure. These restrictions also apply to nintedanib [15].

Another challenge to the guidance came from further post hoc analysis looking at patients who had a decline of ≥10% predicted FVC in the first 6 months of the CAPACITY and ASCEND studies [16]. Ongoing use with pirfenidone significantly reduced the number of patients having a further drop of ≥10% or death in the subsequent 6 months. The authors concluded that ongoing treatment with pirfenidone after a clinical significant decline in FVC still confers prognostic benefit.

3.2 Nintedanib

A subgroup analysis of the pooled data from the INPULSIS trials was performed, examining prespecified groups based on a variety of characteristics, including sex, age, race, smoking status and baseline percentage predicted FVC (≤70 or >70%) [17]. The results showed a consistent treatment effect across all subgroups, with no significant difference between them. The authors concluded that nintedanib is effective across all IPF phenotypes. Similar results were found in patients with definite versus possible usual interstitial pneumonia (UIP) pattern of IPF [18]. The INPULSIS data were also examined to assess the benefit of nintedanib in patients with preserved lung function, defined as percentage predicted FVC of ≥90% [19]. Overall, 274 of the 1061 patients in the trial had percentage predicted FVC of ≥90%. Both groups gained significant benefit from nintedanib in reducing absolute FVC decline and disease progression. There was no difference between the groups, suggesting that nintedanib is equally effective in patients with less severe disease. As with pirfenidone, this challenges NICE guidelines that restrict use to patients with FVC <80% predicted. In many European countries and the US, there is no upper limit to commencement of antifibrotics in IPF and early commencement is possible in order to impact disease progression in an otherwise devastating and life-limiting disease.

Table 1 summarises the findings from the post hoc studies for both pirfenidone and nintedanib.

4 Safety and Tolerability

Pirfenidone and nintedanib both have side effect profiles that require careful education and management to maintain adherence and maximise efficacy, particularly in a symptomatic comorbid and elderly population.

4.1 Pirfenidone

In the pooled analysis of the CAPACITY and ASCEND studies, 11.9% of patients discontinued pirfenidone due to treatment-emergent adverse events, compared with 8.7% of patients receiving placebo [10]. Common adverse events included nausea (35.5%), diarrhoea (24.6%), photosensitivity rash (29.2%) and fatigue (23%). A significant rise in liver function tests, which reversed with discontinuation of therapy, was seen in 3.2% of patients. Reassuringly, real-world data appear to match the experimental findings, with similar adverse events reported. In a study of 351 patients taking pirfenidone, 78% of patients had at least one adverse event [20]. Of all adverse events reported, 75% were gastrointestinal in origin. The majority of patients continued treatment, with 49% of patients managing their side effects with no change in treatment, while 16% required a dose reduction. The discontinuation rate was slightly higher than in the phase III studies (20 vs. 11.9%), likely due to the longer duration of treatment and patients who were older and more comorbid in the real-world setting. Patients who discontinued treatment tended to have a lower DLCO, although there was no difference in baseline FVC or other characteristics such as age or body mass index (BMI) in this study. Similar outcomes have been reported elsewhere in the real-world clinical setting [21–23].

Pirfenidone is contraindicated in patients with a creatinine clearance (CrCl) of <30 mL/min. It is metabolised by cytochrome P450 (CYP) 1A2 and interacts with drugs that use this pathway. Cigarette smoke can potentiate the metabolism of pirfenidone through CYP1A2, making it less effective; therefore, it is recommended that patients stop smoking prior to or on initiation of treatment [24]. Pirfenidone is manufactured as 267 mg capsules. Treatment is titrated over a 2-week period to provide an optimum dose of three capsules, three times daily (total daily dose of 2403 mg). The divided dose format allows dose reductions and re-titration to manage adverse events. Some patients may find the pill burden challenging, however a new formulation with an 801 mg capsule may help to alleviate this. To reduce the risk of photosensitive rash, patients are advised to protect themselves from direct sunlight.

Table 1 Summary of results from post hoc studies of pirfenidone and nintedanib

	Pirfenidone [$N = 1247$][a]			Nintedanib [$N = 1061$]		
	Post hoc study	Treatment benefit vs. placebo[g]	Difference within treatment group	Post hoc study	Treatment benefit vs. placebo[g]	Difference within treatment group
Mortality	Nathan et al., 2017 [11]	Yes	NA	–	–	–
Continued treatment after lung function decline	Nathan et al., 2016 [16]	Yes	NA	–	–	–
Preserved lung function[b]	Albera et al., 2016 [12]	Yes	Yes[g,h]	Kolb et al., 2017 [19]	Yes	No
Reduced lung function[c]	Noble et al., 2016 [10]	Yes	No	Costabel et al., 2016 [17]	Yes	No
Pattern of disease (definite vs. possible UIP)	–	–	–	Raghu et al., 2017 [18]	Yes	No
Baseline characteristics						
Sex	Noble et al., 2016 [10]	Yes	No	Costabel et al., 2016 [17]	Yes	No
Age[d]		Yes	No		Yes	No
Smoking status[e]		Yes	No		Yes	No
Race/ethnicity[f]		Yes	No		Yes	No

N total number of patients included in the primary trials [6, 7, 9], *NA* not applicable, *FVC* forced vital capacity, *UIP* usual interstitial pneumonia

[a] Pooled data set from the CAPACITY and ASCEND trials [6, 7]

[b] Defined as FVC ≥80% for pirfenidone and >90% for nintedanib

[c] Defined as FVC <65% for pirfenidone and ≤70% for nintedanib

[d] Age split into <65, 65–74 and ≥75 years for pirfenidone, and <65 vs. ≥65 years for nintedanib

[e] Never smoked vs. current/ex-smoker

[f] White vs. Non-White for pirfenidone, White vs. Asian for nintedanib

[g] Statistical significance at $p < 0.05$

[h] Patients with preserved lung function less likely to have ≥10% decline in FVC or death at 12 months

4.2 Nintedanib

In the INPULSIS trials, 19.3% of patients taking nintedanib discontinued treatment due to adverse events, compared with 13% of patients receiving placebo [9]. Diarrhoea was common, with 62.4% of patients reporting at least mild diarrhoea; however, only 4.4% of patients discontinued treatment as a result of this adverse event. Other common adverse events included nausea (24.5%) and nasopharyngitis (13.6%). Significantly higher numbers of patients had elevation of liver enzymes as a result of nintedanib treatment. VEGF receptor inhibition has been associated with both thrombosis and haemorrhage [25], therefore patients with a recent history of unstable ischaemic heart disease or those receiving full-dose anticoagulation or high-dose antiplatelets were excluded. The frequency of cardiac events and serious bleeding in the INPULSIS trials was low. Similar rates of adverse events were observed in the 'real-world' study of nintedanib use [20]. Treatment was discontinued in 26% of patients due to side effects, and 15% required a dose reduction; 57% suffered at least one adverse event related to diarrhoea, while 71% of these patients continued with treatment unchanged.

Nintedanib is supplied as 150 mg capsules taken twice daily; however, a reduced dose of 100 mg twice daily can be used for patients intolerant of the higher strength. The manufacturer recommends that nintedanib should be avoided in patients requiring full-dose anticoagulation [26]. Both nintedanib and pirfenidone require close monitoring of liver function tests.

5 Putting the Evidence into Context: Does the Trial IPF Population Reflect Reality?

Patients in clinical trials are often younger and have less comorbidities compared with the real-world setting [20]. So how representative are these findings of the real-world IPF population? The average age for patients presenting with IPF from registry data is 68.7–73.5 years, and 18% of patients are over the age of 80 years [13, 27–30]. In the pirfenidone trials, the upper age limit was 80 years and the

mean age was 68 years [10], while in the INPULSIS trials, the mean age for the nintedanib population was younger, at 66.7 years [9]. Post hoc analysis has suggested that there is no difference in the efficacy of antifibrotics with respect to age [10, 16]. A recent real-world study has suggested that patients are more likely to discontinue antifibrotic therapy due to adverse effects and disease burden if they are aged 70 years or above [21].

The antifibrotic studies limited inclusion to patients with an FVC of at least 50% predicted, excluding patients with severe disease [6, 7, 9]. The BTS registry data suggest that 4% of patients with IPF have an FVC of <50% predicted at first presentation [13]. The impact of antifibrotics on this severe group of patients in still unknown. The clinical trials with pirfenidone also placed an upper limit of percent predicted FVC at 90%. In the INPULSIS trials, 25% of patients had an FVC of ≥90% predicted [9], while in the UK, 39% of patients have an FVC of ≥80% predicted, which is outside the regulatory limits of antifibrotic treatment, as depicted by NICE [13]. In the real-world setting, patients prescribed antifibrotic therapies have severer disease, as depicted by lower FVC and DLCO, compared with the clinical trials [20].

Chronic obstructive pulmonary disease (COPD) is a common comorbidity of IPF patients, being reported in up to 36% of cases [27]. Given the overlap in symptoms, the true extent of combined disease is unclear. The incidence of combined pulmonary fibrosis and emphysema syndrome (CPFE) varies, but the presence of emphysema on computed tomography (CT) scan in patients with IPF has been reported to be as high as 51% [31]. The antifibrotic therapeutic trials attempted to exclude COPD/emphysema to produce a purer IPF population. The CAPACITY studies only excluded patients if they had a physician diagnosis of COPD, without placing any restriction based on physiological parameters or radiological evidence of emphysema [6]. The ASCEND study excluded patients with a forced expiratory volume in 1 s (FEV1)/FVC ratio of <0.8 and patients with predominant emphysema on high resolution CT (HRCT) [7]. In the INPULSIS trials, patients were excluded if they had an FEV1/FVC ratio of <0.7. Patients with emphysema were not excluded, therefore a number of patients with CPFE are likely to have been treated [9]. The impact of antifibrotics on patients with combined emphysema and fibrosis is largely unknown due to these trial restrictions.

6 Important Considerations for Clinical Decision Making

Given the absence of head-to-head data comparing pirfenidone and nintedanib, and the favourable clinical outcomes demonstrated in both the primary phase III clinical trials and subsequent post hoc studies, decisions regarding which antifibrotic to choose will generally be guided by shared decision making between the patient and clinician, taking into account information regarding adverse effect profiles, pill burden and tolerability. The more informed a patient is about the benefits of treatment, the potential adverse events and how these can be managed practically, can ultimately improve patient adherence and confidence in their treatment goals. Many adverse effects are tolerable or can be managed by ensuring antifibrotics are not taken on an empty stomach, through dose reduction or with the addition of other treatments, e.g. antiemetics or antidiarrhoeal treatment. Specialist nurses and support strategies such as *IPF Care* provide a key resource and support for patients [32]. Patients not only welcome support regarding antifibrotic side effect management but also discussions regarding oxygen, pulmonary rehabilitation and palliative care.

Manufacturers recommend clinicians avoid pirfenidone in patients with severe renal impairment (CrCl <30), and avoid nintedanib in patients with active cardiovascular disease. The mechanism of action of nintedanib and its effect on VEGF has raised concerns regarding cardiovascular risk; however, to date, real-world data have been reassuring and have not demonstrated any adverse cardiovascular signals [20, 21]. Further evidence is required to assess this concern. The manufacturer's recommendation to avoid its use in those taking anticoagulation is also questionable and only real-world data will help in addressing this.

Patients may choose one antifibrotic over another, depending on their unique lifestyle choices and preferences. For example, the potential risk of a photosensitive rash may not be acceptable for a patient who spends a lot of time outdoors. Conversely, some patients may prefer not to risk the chance of loose stools or diarrhoea. Ultimately, it is important that patients make informed decisions with accurate dialogue with their healthcare physicians regarding prognostic aims of treatment and the ability to manage side effects effectively and confidently.

Real-world data highlight the safety and tolerability of antifibrotic treatment [20–23]; however, it is not clear how best to manage patients who do not tolerate or suffer disease progression on one of the antifibrotics. A small case series reported that switching patients from pirfenidone to nintedanib, either due to disease progression or poor tolerance, led to disease stability [33]. Case studies have been published suggesting that combination therapy with pirfenidone and nintedanib may help to achieve disease stability, and is well tolerated; however, robust evidence from randomised control trials is required before this can be considered as a safe treatment option [34–36].

Clinical trial data suggest that antifibrotics may have an important role in limiting disease progression and mortality in IPF [6, 7, 9, 11]. Despite these positive findings, it seems to be apparent that there is a large volume of patients who are not currently receiving antifibrotic therapy. A large European physician questionnaire identified that of 1783 patients, 54% were not currently receiving antifibrotic treatment [37]. The reasons for these decisions need to be explored further, however patients appeared to be older and have 'milder' disease. Post hoc analysis and real-world data have indicated that age does not appear to be a barrier to the benefit of antifibrotic treatment, and, on the whole, it can be tolerated by careful education and support [10, 16, 20]. The concept of 'mild' disease based purely on FVC measurement also needs to be challenged. An FVC of ≥80% would traditionally be classified as 'mild' disease, however lung function alone does not appear to be sufficient at predicting the clinical course of IPF [38]. Clinical scoring systems, such as the Gender, Age and Physiology (GAP) index, which take into consideration both clinical and physiological variables, may allow better prognostic stratification [39]. As such, limiting prescription of antifibrotic therapy to patients based on FVC alone, as is the case in the UK, may be short-sighted, particularly given that 39% of patients with IPF in the UK present with an FVC >80% [13]. In theory, in a disease with otherwise extremely poor outcomes, starting antifibrotic therapy in early disease to have the maximum benefit may also provide significant survival benefit, although further robust data are needed to support this.

7 Conclusion

The primary data and subsequent post hoc studies support pirfenidone and nintedanib as effective treatments for many patients with IPF regardless of age, and physiological- and disease-related characteristics. Real-world data complement the clinical trials to demonstrate that, on the whole, antifibrotics in IPF are safe and tolerable with careful specialist education and management. In the absence of head-to-head comparison data, neither drug shows superiority in efficacy, therefore patient choice and suitability should be the driving force behind drug selection.

Author Contributions Conal Hayton planned, drafted and approved the final version of the submitted manuscript. Nazia Chaudhuri planned, critically appraised and approved the final version of the submitted manuscript.

Compliance with ethical standards

Conflict of interest Conal Hayton has not received any payment or funding to produce this article and has no conflict of interests to report. Nazia Chaudhuri has not received any payment or funding to produce this article, but has received a research grant from Boehringer Ingelheim for research in IPF, and has received consultant fees from Boehringer Ingelheim, Roche and Intermune, as well as payment from Roche for lectures delivered.

References

1. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;157(1):199–203.
2. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192(2):e3–19.
3. Oku H, Shimizu T, Kawabata T, et al. Antifibrotic action of pirfenidone and prednisolone: different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. Eur J Pharmacol. 2008;590(1–3):400–8.
4. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Repir Crit Care Med. 2005;171(9):1040–7.
5. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):821–9.
6. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): Two randomised trials. Lancet. 2011;377(9779):1760–9.
7. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92.
8. Wollin L, Wex E, Pautsch A, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J. 2015;45(5):1434–45.
9. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.
10. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. Eur Respir J. 2016;47:243–53.
11. Nathan SD, Albera C, Bradford WZ, Costabel U, et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. Lancet Respir Med. 2017;5:33–41.
12. Albera C, Costabel U, Fagan EA, et al. Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function. Eur Respir J. 2016;48:843–51.
13. The British Thoracic Society Interstitial Lung Disease Registry Programme Annual Report 2015/2016. British Thoracic Society Reports. 2016; 8(2). https://www.brit-thoracic.org.uk/standards-of-care/lung-disease-registries/bts-ild-registry/. Accessed 20 May 2017.
14. National Institute for Health and Care Excellence. Pirfenidone for Treating Idiopathic Pulmonary Fibrosis. TA282. London: NICE; 2013.
15. National Institute for Health and Care Excellence. Nintedanib for Treating Idiopathic Pulmonary Fibrosis. TA379. London: NICE; 2016.
16. Nathan SD, Albera C, Bradford WZ, et al. Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax. 2016;71:429–35.
17. Costabel U, Inoue Y, Richeldi L, et al. Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across prespecified subgroups in INPULSIS. Am J Respir Crit Care Med. 2016;193(2):178–85.

18. Raghu G, Wells AU, Nicholson AG, et al. Effect of Nintedanib in subgroups of Idopathic Pulmonary Fibrosis by diagnosit criteria. Am J Respir Crit Care Med. 2017;195(1):78–85.
19. Kolb M, Richeldi L, Behr J, et al. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. Thorax. 2017;72:340–6.
20. Hughes G, Toellner H, Morris H, et al. Real world experiences: pirfenidone and Nintedanib are effective and well tolerated treatments for idiopathic pulmonary fibrosis. J Clin Med. 2016;5(9):1–12.
21. Galli JA, Pandya A, Vega-Olivio M, et al. Pirfenidone and nintedanib for pulmonary fibrosis in clinical practice: tolerability and adverse drug reactions. Respirology. 2017;22(6):1171–8.
22. Wijsenbeek MS, Grutters JC, Wuyts WA. Early experience of pirfenidone in daily clinical practice in Belgium and The Netherlands: a retrospective cohort analysis. Adv Ther. 2015;32:691–704.
23. Oltmanns U, Kahn N, Wenz H, et al. Pirfenidone in idiopathic pulmonary fibrosis—real life experience from a german tertiary referral centre for interstitial lung diseases. Eur Respir J. 2013;42(Suppl 57):P2335.
24. Genetech USA Inc. Prescribing Information for Esbriet, 2017. https://www.gene.com/download/pdf/esbriet_prescribing.pdf. Accessed 20 May 2017.
25. Kamda T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer. 2007;96(12):1788–95.
26. Boehringer Ingelheim Pharma. Ofev Summary of Product Characteristics. 2015. https://products.boehringer-ingelheim.com/ofev/sites/default/files/OFEV-SMPC.pdf. Accessed 20 May 2017.
27. Jo HE, Glaspole I, Grainge C, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian idiopathic pulmonary fibrosis registry. Eur Respir J. 2017;49(2):1601592.
28. Behr J, Kreuter M, Hoeper MM, et al. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. Eur Respir J. 2015;46(1):186–96.
29. Kaunisto J, Kelloniemi K, Sutinen E, et al. Re-evaluation of diagnostic parameters is crucial for obtaining accurate data on idiopathic pulmonary fibrosis. BMC Pulm Med. 2015;15:92.
30. Ferrara G, Carlson L, Palm A, et al. Idiopathic pulmonary fibrosis in Sweden: report from the first year of activity of the Swedish IPF-Registry. Eur Clin Respir J. 2016;3:31090.
31. Schmidt SL, Nambiar AM, Tayob N, et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. Eur Respir J. 2011;38(1):176–83.
32. Duck A, Pilgrim L, Errhalt P, et al. IPF Care: a support program for patients with idiopathic pulmonary fibrosis treated with pirfenidone in Europe. Adv Ther. 2015;32(2):87–107.
33. Rathnapala A, Fries A, Ruggiero C, et al. Single centre experience of switching patients with idiopathic pulmonary fibrosis from pirfenidone to nintedanib. Thorax. 2016;71(Suppl 3):S101.
34. Ikeda S, Sekine A, Baba T, et al. Administration of nintedanib after discontinuation for acute exacerbation of idiopathic pulmonary fibrosis: a case report. BMC Pulm Med. 2016;16:38.
35. Hagmeyer L, Treml M, Priegnitz C, Randerath WJ. Successful concomitant therapy with pirfenidone and nintedanib in idiopathic pulmonary fibrosis: a case report. Respiration. 2016;91(4):327–32.
36. Taniguchi H, Ogura T, Inoue Y et al. Long-term safety of combination therapy with nintedanib and pirfenidone in Japanese patients with IPF. Eur Respir J. 2016;48(Suppl 60):PA2089.
37. Maher TM, Molina-Molina M, Russell AM, et al. Unmet needs in the treatment of idiopathic pulmonary fibrosis (IPF)—insights from patient chart review in five European countries. Thorax. 2016;71(Suppl 3):P161.
38. Ley B, Collard HR, King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:431–40.
39. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012;156:684–91.