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STUDY PROTOCOL

The Design and Rationale of the Trail1 Trial: A Randomized Double-Blind Phase 2 Clinical Trial of Pirfenidone in Rheumatoid Arthritis-Associated Interstitial Lung Disease

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is the most common of the connective tissue diseases (CTD), affecting up to 0.75% of the United States (U.S.) population with an increasing prevalence. Interstitial lung disease is prevalent and morbid condition in RA (RA-ILD), affecting up to 60% of patients with RA, leading to premature death in 10% and accruing an average of US$170,000 in healthcare costs per patient over a 5-year period. Although there have been significant advances in the management of this joint disease, there are no ongoing randomized clinical trials looking at pharmacologic treatments for RA-ILD, and there currently are no U.S. Food and Drug Administration-approved drugs for RA-ILD.

Methods/Design: We describe the Treatment for Rheumatoid Arthritis and Interstitial Lung Disease 1 (TRAIL1) trial, a multicenter randomized, double-blind, placebo-controlled, phase 2 study of the safety, tolerability and efficacy of pirfenidone in patients with RA-ILD. The study will enroll approximately 270 subjects across a network of sites who have RA and ILD as defined by a fibrotic abnormality involving greater than 10% of the lung parenchyma. The primary endpoint of the study is the incidence of the composite endpoint of decline in percent predicted forced vital capacity of 10 or greater or death during the 52-week study period. A number of secondary and exploratory endpoints have been chosen to

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evaluate the safety and efficacy in different domains.

Discussion: The TRAIL1 trial is designed to evaluate the safety and efficacy of pirfenidone in RA-ILD, a disease with significant impact on patients' quality of life and outcome. In addition to investigating the safety and efficacy of pirfenidone, this trial looks at a number of exploratory endpoints in an effort to better understand the impact of therapy on areas such as changes in quantitative high-resolution computed tomography scores and a patient's quality of life. Biospecimens will be collected in order to investigate biomarkers that could potentially predict the subtype of disease, its behavior over time, and its response to therapy. Finally, by creating a network of institutions and clinician investigators with an interest in RA-ILD, this trial will pave the way for future studies of investigational agents in an effort to reduce or eliminate the burden of disease for those suffering from RA-ILD.

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Trial Registration: Clinicaltrials.gov, identifier NCT02808871.

Keywords: Pirfenidone; Rheumatoid; Pulmonary; Fibrosis; Interstitial; Arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is the most common of the connective tissue diseases (CTD). It affects up to 0.75% of the United States (U.S.), and its prevalence is increasing [1]. The global prevalence is 0.24% (or 16 million people), and it ranks as the 42nd highest contributor to global disability [2]. In the U.S. alone, the annual excess health cost related to RA is estimated at US$19.3 billion [3].

RA has a variety of extra-articular manifestations that lead to increased morbidity and mortality. The respiratory system is commonly involved and, notably, all of its components are susceptible [4]. Interstitial lung disease (ILD) is a dreaded complication of RA, leading to excess morbidity and mortality. The prevalence of RA-related ILD (RA-ILD) in unselected patients ranges from 19 to 63% [5], with a lifetime risk in any one patient of 7.7% [6]. Unlike many other forms of CTD-ILD, RA-ILD is most frequently associated with a usual interstitial pneumonia pattern of pathology, the same pattern seen in idiopathic pulmonary fibrosis (IPF). This similarity has led to speculation that therapeutic agents with efficacy in IPF might also have efficacy in RA-ILD.

Pirfenidone is a novel compound with both anti-inflammatory and anti-fibrotic properties. It is effective in several animal models of fibrosis [7] and has been studied in 15 controlled or uncontrolled clinical trials in human subjects with pulmonary fibrosis [8–22]. It has been approved in several countries for the treatment of patients with IPF based on phase 3 clinical trial results [14].

This manuscript describes the design of the Treatment for Rheumatoid Arthritis and Interstitial Lung Disease 1 (TRAIL1) Trial, a multicenter randomized, double-blind, placebo-controlled, phase 2 study of the safety, tolerability and efficacy of pirfenidone in patients with RA-ILD.

METHODS/DESIGN

The TRAIL1 trial is a 52-week trial whose objectives are listed in Table 1. It is being conducted in the United States, the United

Table 1 Study objectives

TRAIL1 study objectives
1. To assess the efficacy and safety of pirfenidone 2403 mg/day as compared to placebo in patients with RA-associated interstitial lung disease
2. To explore the role of peripheral blood biomarkers in predicting disease progression and survival in patients with RA-associated interstitial lung disease
3. To explore a spectrum of validated questionnaires to assess disease specific PROs including overall health, and perspectives on symptoms, performance and quality of life

Kingdom, Canada and Australia at sites recognized as centers of excellence in the management of patients with ILD. Approximately 270 subjects meeting eligibility criteria for the study will be randomized to receive either pirfenidone 2403 mg/day or placebo. Safety will be assessed by determining differences between the treatment arms for the rate of adverse events and serious adverse events. Efficacy will be evaluated through interval testing of pulmonary function tests, patient-reported outcomes (PROs) and survival occurring during 11 study visits over 52 weeks.

Patient Population

Eligible patients aged 18–85 years must meet 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA [23]. RA-ILD will be diagnosed by imaging and, when available, surgical lung biopsy (SLB). On initial screening (and confirmed by a centrally-adjudicated expert read), high-resolution computed tomography (HRCT) scans must have the presence of fibrotic abnormality affecting more than 10% of the lung parenchyma, with or without traction bronchiectasis or honeycombing. There must be no evidence or suspicion of an alternate diagnosis and no features supporting an alternate diagnosis on transbronchial biopsy or SLB if performed prior to screening.

Patients will be required to have a percent predicted forced vital capacity (FVC%) $\geq$40 and percent predicted diffusing capacity of the lung for carbon monoxide (DLCO%) $\geq$30 at screening as well as $<$ 10% relative change in pre-bronchodilator FVC between screening (Visit 1) and baseline (Visit 2). Any patient identified for the study must discontinue all prohibited therapies for at least 28 days before the start of screening. The screening period may last up to 56 days.

Exclusion Criteria

A full list of inclusion and exclusion criteria are listed in Supplemental Table 1. There are exclusions that ensure a well-phenotyped cohort of RA-ILD (i.e., excluding other CTDs, overlap syndromes or other potential causes of ILD). Also excluded are patients with certain concomitant conditions such as other lung manifestations of RA, human immunodeficiency virus, viral hepatitis or other liver diseases leading to hepatic dysfunction, clinically significant asthma/chronic obstructive pulmonary disease, active infection, malignancy, end-stage renal disease or unstable cardiac disease (arrhythmias, myocardial infarctions or congestive heart failure). Patients who have the introduction or dose alteration of corticosteroids or any cytotoxic, immunosuppressive, cytokine-modulating or receptor antagonist agent for the management of pulmonary manifestations of RA within 3 months will be excluded. The introduction or dose alteration of agents for extrapulmonary manifestations of RA is not an exclusion.

Study design (Fig. 1)

The study will enroll 270 patients across the network. After written informed consent is obtained, patients will be randomized to pirfenidone or placebo in a 1:1 ratio. Study treatment (defined as either pirfenidone or placebo) will be titrated to full dose over 14 days and patients maintained on study treatment for the duration of the trial (52 weeks). There will be a total of 11 in-person visits and an end-of-study phone call.

Endpoints/Outcomes

The primary endpoint of the study is the incidence of the composite endpoint of decline in predicted FVC% of 10 or greater or death during the 52-week study period. There are a number of secondary endpoints listed in Supplemental Table 2. We will examine endpoints recommended by OMERACT (Outcome Measures in Rheumatology), including the frequency of progressive disease (defined by a categorical decline in FVC% and/or DLCO%) [24]. There are a number of endpoints in the domains of physiology (changes in absolute and percent predicted FVC, slope of FVC change, time to 10% change in FVC), health outcomes (hospitalizations, mortality, exacerbations and

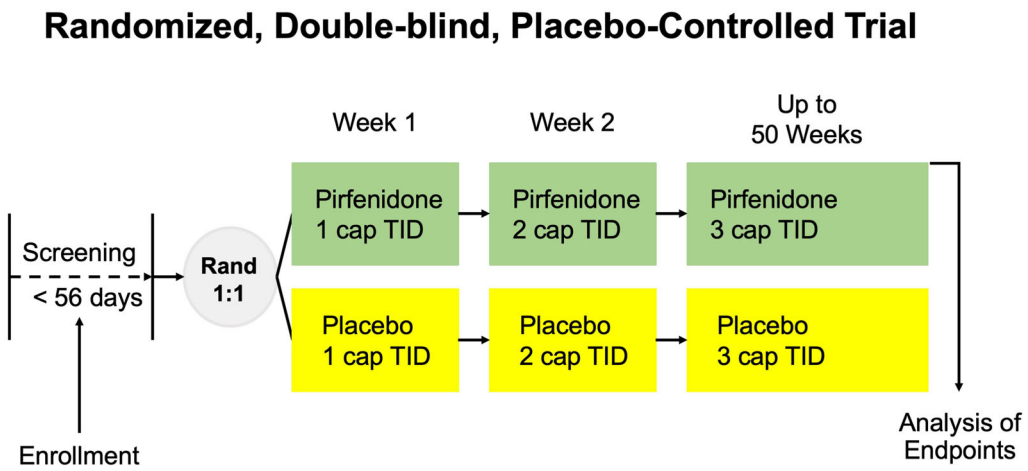

Fig. 1 Trial design

transplant), safety [adverse events (AEs) and serious adverse events (SAEs)] and patient-reported dyspnea, assessed by the Dyspnea-12 questionnaire. Exploratory endpoints include some related to RA disease activity (the Disease Activity Score, the Routine Assessment of Patient Index Data 3 score and the erythrocyte sedimentation rate), biomarker expression, quantitative HRCT scores and PROs including the Leicester Cough Questionnaire, the Patient Global Assessment and the Health Assessment Questionnaire.

Assessment of Safety

The relevant International Conference on Harmonization guidelines, the latest European Union Pharmacovigilance guidelines and applicable European Union legislation, the U.S. Code of Federal Regulations, Title 21, and relevant local regulations form the basis of the information to be exchanged under this protocol and to be reported to the regulatory authorities, as applicable.

Site investigators are responsible for monitoring the safety of the participants who enter the study and will collect and track all protocol-defined AEs and pregnancy reports from the Study. They will also track all serious adverse drug reactions. SAEs will be reported to the trial sponsor via the Data Coordinating Center. The severity of AEs will be determined by pre-set guidelines. The investigator remains responsible for the medical management of AEs and SAEs. The blind will be broken for adverse drug reaction reports that are serious and unexpected, unless otherwise agreed upon with applicable regulatory authorities.

Sample Size Calculation and Statistical Analysis

Hypothesized estimates of treatment response in both placebo and pirfenidone arms were derived from a trial of Pirfenidone in IPF [14]. If participants with RA-ILD are similar, then a sample size of 254 participants (127 per group) will provide 85% power to demonstrate the treatment difference in the combined primary endpoint by week 52. To account for dropout or loss-to-follow-up, 270 subjects will be enrolled.

The primary efficacy endpoint will be analyzed by using logistic regression. We will conduct univariate between-groups comparisons of time to the primary efficacy endpoint. Kaplan–Meier plots will be generated, and curves will be compared using the log-rank test. Multivariate time-to-event analyses will be conducted by using Cox proportional hazards regression models; here, treatment group will be the main effect variable and potentially influential confounders will be added to assess their influence on the outcome. Similar analyses will be run for the individual components of the primary endpoint and for the secondary and exploratory endpoints.

Trial Oversight

Oversight will be under the direction of a Data Safety and Monitoring Board (DSMB), which is composed of individuals with expertise in RA-ILD, the study drugs and clinical trials research. It includes experts in Rheumatology, Pulmonary Medicine, Internal Medicine and/or Bioethics, and Biostatistics. The DSMB will meet every 6 months and will review adverse effects and monitor the performance of individual clinics and study performance indicators. They will provide external oversight concerning the safety and scientific integrity of the trial. This trial is designed in accordance with the Standard Protocol Items for Clinical Trials (SPIRIT) 2013 statement and will be carried out in compliance with the ethical principles of the Declaration of Helsinki. All documents are initially approved by the institutional review board (IRB) at the sponsor site (BWH) and then by the individual IRBs or competent authorities at the individual sites. For a full list of the individual IRBs, please see the Supplementary Material. Written informed consent will be obtained from all participants before any study-related procedures are implemented.

DISCUSSION

Rationale for Studying Pirfenidone in this Disease Process

ILD is a common manifestation of RA. RA affects 0.29–0.31% of males and 0.73–0.78% of females in the U.S. population [1]; up to 63% of the RA population will have radiographic evidence of ILD, and, in nearly 10%, ILD will contribute to mortality [25]. Radiographic progression occurs in 60% of patients over an 18-month period [26], and patients with clinically significant RA-ILD have an average lifespan of 2.6 years compared to 10 years in age-matched RA patients without ILD [6]. In addition to shortening lifespan, ILD has an impact on quality of life, with RA-ILD patients scoring the same or worse on the Short Form Health Survey (SF-36) when compared to those with IPF, a disease with progressive respiratory failure and an average lifespan after diagnosis of 3.6 years [27]. RA-ILD also has a significant impact on healthcare costs, with an estimated mean 5-year cost of US$173,000 per patient [28].

Although scientific advances in the last decade have led to significant improvements in the control of the joint disease in RA, the management of the lung disease has not enjoyed similar progress. There are currently no Food and Drug Administration (FDA)-approved therapies for RA-ILD; no other phase 2 or 3 trials for RA-ILD have been completed, and, to our knowledge, none are recruiting at the time of this manuscript. The lack of data to guide clinicians and the absence of reliably effective therapies for RA-ILD are well-recognized gaps [29–32]. The American Thoracic Society (ATS) Working Group on Pulmonary Fibrosis recently identified the establishment of a clinical research center network to test promising compounds in pulmonary fibrosis as a priority [33]. For these reasons, we chose to evaluate a plausible therapy for patients suffering from RA-ILD.

Rationale for the Chosen Agent

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) is an agent with known antifibrotic and anti-inflammatory properties and activity against pulmonary, renal, hepatic and cardiac fibrosis [7, 34, 35]. It reduces transforming growth factor-beta (TGF-β) [7], counteracts the TGF-β-induced pro-fibrotic effects of human fibroblasts through inhibition of extracellular signal-regulated kinase 1/2 [36] and inhibits epithelial–mesenchymal transition [37].

Based on multiple studies involving over 1300 patients, the FDA approved pirfenidone for treatment of IPF in 2014 [8–14]. RA-ILD holds many similarities to IPF, including often indistinguishable imaging [38] and overlapping histopathological features of fibrosis, fibroblastic foci, temporal heterogeneity, and traction bronchiolectasis [39]. Several studies suggest a similar survival between RA-ILD and IPF [40, 41], although, in a more recent study, survival was longer for RA-ILD [42]. These similarities led the TRAIL network to design a trial to

evaluate an agent with proven efficacy in IPF in patients with RA-ILD.

Rationale for the Trial Design

We decided to include only patients with at least 10% parenchymal involvement on HRCT to enrich the cohort with patients at a higher risk of progression. It is unclear if patients with milder disease have a similar progression over time, and our ability to predict outcome in this cohort is limited [31]. The dose of pirfenidone 2403 mg/day was chosen as the dose shown in studies of pirfenidone in IPF to have favorable efficacy and safety results compared with placebo [14].

Rationale for the Endpoints

Multiple authors have reported that a decrement in FVC% over 6–12 months, particularly if $\geq$ 10% in magnitude, is both clinically significant and highly predictive of mortality [43–45]. The primary endpoint combines this clinically-meaningful change in FVC with death, another clinically relevant endpoint. Composite endpoints allow the assessment of important outcomes in smaller-sized study samples.

The secondary endpoints look at a number of different variables intended to demonstrate an effect of pirfenidone on other meaningful outcomes. Safety variables are included in the secondary endpoints. The exploratory endpoints, focused on extrapulmonary aspects of RA, were chosen to obtain a better understanding of the impact of therapy on joint disease and to test the validity and responsiveness of changes in PROs.

Development of a Research Network

In addition to testing the safety and efficacy of pirfenidone in RA-ILD, this trial provides the platform for the development of research network composed of sites of excellence in the diagnosis and management of RA-ILD. This network will facilitate the development of multi-center collaborative studies and future clinical trials designed to decrease the significant morbidity and mortality associated with RA-ILD [29]. We will create a multi-national research platform capable of collecting, storing, and distributing clinically annotated patient-derived samples in an open-access biorepository, including detailed exposure and clinical information as outlined by the recent ATS Research Statement on Future Directions in Lung Fibrosis Research [33]. We will have a well-phenotyped cohort of patients with RA-ILD to help facilitate future translational and clinical trials. This trial will also facilitate the creation of an ongoing RA-ILD registry and a biobank of clinical specimens. The registry will serve the purpose of improving our understanding of the natural history of the disease, as well as providing subjects for future studies. A biobank of clinical specimens is critical to exploring candidate biomarkers in an effort to learn more about predictors of disease, disease behavior over time, and response to therapy.

Strengths and Limitations

The strength of this trial lies in the trial design and patient population. This trial is designed to look at a number of clinical variables in order to broadly capture a potential treatment effect. The exploratory endpoints allow us to investigate the impact of therapy on the way the patient feels, a critically important endpoint that is often excluded from large clinical trials.

This is a well-phenotyped patient population. We have eliminated potential cofounders by excluding secondary Sjogren's and overlap syndromes, as well as any other potential contributors to ILD. To select for a population at risk for progression, and therefore a likely benefit from treatment, we require at least 10% involvement of the lung by reticulation.

The weaknesses of this study include the selection of a patient population that presents unique recruitment challenges. By having a connective tissue disease in addition to a lung disease, these subjects have frequent interactions with the healthcare system and are often reluctant to participate in a trial that adds to the burden of their ongoing healthcare. In addition

to recruitment challenges, we do not require evidence of progression of lung disease at baseline or any minimal level of RA activity which could potentially lead to the recruitment of stable patients, diluting a possible treatment effect.

In conclusion, the TRAIL1 trial is the first placebo-controlled trial for patients with RA-ILD and will evaluate the safety and efficacy of pirfenidone as well as its effect on a number of primary, secondary, and exploratory endpoints. In addition to evaluating a potentially efficacious treatment, it will create a research network that will lead the way to a better understanding of RA-ILD and an improved quality of life for those suffering from this disease.

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Trial Registration. The trial is registered with Clinicaltrials.gov, identifier NCT02808871.

Authorship. All named authors meet the International Committee of Medical Journal. Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. JJS, SKD, HJG, CS, SH, PFD and IOS contributed to the conception and design of the study and developed the study protocol, JJS, FW, MK and DCC are responsible for the recruitment of subjects, DD, SHH and EBP are responsible for the management of the trial and DD, CS and SH are responsible for collection and analysis of the data. All authors contributed to modification of the original protocol and all authors read and approved the final manuscript.

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Compliance with Ethics Guidelines and dissemination. This trial is designed in accordance with the Standard Protocol Items for Clinical Trials (SPIRIT) 2013 statement and will be carried out in compliance with the ethical principles of the Declaration of Helsinki. All documents are initially approved by the institutional review board (IRB) at the sponsor site (BWH) and then by the individual IRBs or competent authorities at the individual sites. Written informed consent will be obtained from all participants before any study-related procedures are implemented. When available, the results will be published in an international peer-reviewed journal.

REFERENCES

1. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. Rheumatol Int. 2017;37(9):1551–7.

2. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316–22.

3. Birnbaum H, Pike C, Kaufman R, Marynchenko M, Kidolezi Y, Cifaldi M. Societal cost of rheumatoid arthritis patients in the US. Curr Med Res Opin. 2010;26(1):77–90.

4. Brown KK. Rheumatoid lung disease. Proc Am Thorac Soc. 2007;4(5):443–8.

5. Demoruelle MK, Solomon JJ, Olson AL. The epidemiology of rheumatoid arthritis-associated lung disease. In: Fischer A, Lee JS, editors. Lung disease in rheumatoid arthritis. 1st ed. Totowa: Humana; 2018. p. 45–58.

6. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62(6):1583–91.

7. Schaefer CJ, Ruhrmund DW, Pan L, Seiwert SD, Kossen K. Antifibrotic activities of pirfenidone in animal models. Eur Respir Rev. 2011;20(120):85–97.

8. Nagai S, Hamada K, Shigematsu M, Taniyama M, Yamauchi S, Izumi T. Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. Intern Med. 2002;41(12):1118–23.

9. Raghu G, Johnson WC, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. Am J Respir Crit Care Med. 1999;159(4 Pt 1):1061–9.

10. Gahl WA, Brantly M, Troendle J, et al. Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome. Mol Genet Metab. 2002;76(3):234–42.

11. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171(9):1040–7.

12. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):821–9.

13. 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.

14. 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.

15. Huang H, Dai HP, Kang J, Chen BY, Sun TY, Xu ZJ. Double-blind randomized trial of pirfenidone in Chinese idiopathic pulmonary fibrosis patients. Medicine (Baltimore). 2015;94(42):e1600.

16. Costabel U, Albera C, Bradford WZ, et al. Analysis of lung function and survival in RECAP: an open-label extension study of pirfenidone in patients with idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31(3):198–205.

17. Ogura T, Taniguchi H, Azuma A, et al. Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2015;45(5):1382–92.

18. Behr J, Bendstrup E, Crestani B, et al. Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med. 2016;4(6):445–53.

19. Khanna D, Albera C, Fischer A, et al. An open-label, phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. J Rheumatol. 2016;43(9):1672–9.

20. Iwata T, Yoshino I, Yoshida S, et al. A phase II trial evaluating the efficacy and safety of perioperative pirfenidone for prevention of acute exacerbation of idiopathic pulmonary fibrosis in lung cancer patients undergoing pulmonary resection: west Japan Oncology Group 6711 L (PEOPLE Study). Respir Res. 2016;17(1):90.

21. Vancheri C, Kreuter M, Richeldi L, et al. Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis. Results of the INJOURNEY trial. Am J Respir Crit Care Med. 2018;197(3):356–63.

22. Costabel U, Albera C, Lancaster LH, et al. An open-label study of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (RECAP). Respiration. 2017;94(5):408–15.

23. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.

24. Khanna D, Mittoo S, Aggarwal R, et al. Connective tissue disease-associated interstitial lung diseases (CTD-ILD)—report from OMERACT CTD-ILD Working Group. J Rheumatol. 2015;42(11):2168–71.

25. Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med. 2011;183(3):372–8.

26. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med. 2008;168(2):159–66.

27. Natalini JG, Swigris JJ, Morisset J, et al. Understanding the determinants of health-related quality

of life in rheumatoid arthritis-associated interstitial lung disease. Respir Med. 2017;127:1–6.

28. Raimundo K, Solomon JJ, Olson AL, et al. Rheumatoid arthritis-interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. J Rheumatol. 2018.

29. Doyle TJ, Lee JS, Dellaripa PF, et al. A roadmap to promote clinical and translational research in rheumatoid arthritis-associated interstitial lung disease. Chest. 2014;145(3):454–63.

30. Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest. 2009;136(5):1397–405.

31. Assayag D, Lubin M, Lee JS, King TE, Collard HR, Ryerson CJ. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. Respirology. 2014;19(4):493–500.

32. Solomon JJ, Fischer A. Rheumatoid arthritis interstitial lung disease: time to take notice. Respirology. 2014;19(4):463–4.

33. White ES, Borok Z, Brown KK, et al. An American thoracic society official research statement: future directions in lung fibrosis research. Am J Respir Crit Care Med. 2016;193(7):792–800.

34. Choi K, Lee K, Ryu SW, Im M, Kook KH, Choi C. Pirfenidone inhibits transforming growth factor-beta1-induced fibrogenesis by blocking nuclear translocation of Smads in human retinal pigment epithelial cell line ARPE-19. Mol Vis. 2012;18:1010–20.

35. Datta A, Scotton CJ, Chambers RC. Novel therapeutic approaches for pulmonary fibrosis. Br J Pharmacol. 2011;163(1):141–72.

36. Hostettler K, Papakonstantinou E, Klagas I, et al. Anti-fibrotic effects of pirfenidone in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. Eur Respir J. 2015;46(suppl 59):PA3040.

37. Guo J, Yang Z, Jia Q, Bo C, Shao H, Zhang Z. Pirfenidone inhibits epithelial-mesenchymal transition and pulmonary fibrosis in the rat silicosis model. Toxicol Lett. 2018;300:59–66.

38. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2010;35(6):1322–8.

39. Lee HK, Kim DS, Yoo B, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest. 2005;127(6):2019–27.

40. Park JH, Kim DS, Park IN, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease–related subtypes. Am J Respir Crit Care Med. 2007;175(7):705–11.

41. Solomon JJ, Ryu JH, Tazelaar HD, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). Respir Med. 2013;107(8):1247–52.

42. Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2016;47(2):588–96.

43. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168(5):538–42.

44. Flaherty KR, Andrei AC, Murray S, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med. 2006;174(7):803–9.

45. Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):830–6.