# Rationale for the Evaluation of Nintedanib for the Treatment of Systemic Sclerosis-Associated Interstitial Lung Disease

Lutz Wollin[1], Jörg Distler[2], Christopher Denton[3], Martina Gahlemann[4]

[1]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [2]University of Erlangen-Nuremberg, Erlangen, Germany; [3]Royal Free Hospital and UCL Division of Medicine, London, UK; [4]Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland

## Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease of unknown etiology associated with high morbidity and mortality [Rubio-Rivas 2014; Allanore 2015; Denton 2017]. The pathogenesis of SSc is characterized by systemic (multi-organ) immunological, vascular and fibrotic abnormalities [Allanore 2015]. SSc is highly heterogeneous in its manifestations and clinical course [Allanore 2015; Denton 2017]. Skin thickening, sclerosis and ulceration, particularly of the fingers, are common and can cause considerable disability [Hudson 2008; Matucci-Cerinic 2016], while the disease can also affect the pulmonary, cardiovascular, esophageal/gastrointestinal, musculoskeletal, and renal systems [Denton 2017]. Interstitial lung disease and pulmonary arterial hypertension are the most common causes of death related to SSc [Tyndall 2010]. In a *meta*-analysis of data from 13,529 patients published in 2014, survival following diagnosis of SSc was estimated to be 74.9% at 5 years and 62.5% at 10 years [Rubio-Rivas 2014].

Systemic sclerosis-related interstitial lung disease (SSc-ILD) is characterized by progressive pulmonary fibrosis, decline in lung function, symptoms of cough and dyspnea, and impairment in health-related quality of life [Baron 2008; Khanna 2011; Jaeger 2016]. SSc-ILD shows similarities to idiopathic pulmonary fibrosis (IPF), a more common progressive fibrosing ILD of unknown cause, in its natural history, but tends to progress more slowly than IPF and to be associated with a non-specific interstitial pneumonia pattern on HRCT rather than usual interstitial pneumonia, as seen in IPF [Herzog 2014]. Acute deteriorations in lung function, known as acute exacerbations, occur in both SSc-ILD and IPF and are associated with very high morbidity and mortality [Tomiyama 2016; Collard 2016].

## Current treatment of SSc

No drugs are approved for the treatment of SSc, but a multitude of drugs are used to treat specific manifestations of SSc and its associated comorbidities [Denton 2017]. Immunosuppressant therapy is most commonly used, in particular glucocorticoids,

cyclophosphamide (CYC), mycophenolate mofetil (MMF) and methotrexate [Walker 2012; Siegert 2016; Adler 2017]. In Scleroderma Lung Study (SLS) I, conducted in 158 patients with SSc-ILD, treatment with CYC for 1 year provided a modest but significant benefit on forced vital capacity (FVC) per cent predicted versus placebo, as well as improvements in dyspnea and skin thickening [Tashkin 2006]. However, the use of CYC is limited due to its toxicity. In Scleroderma Lung Study II (SLS II), in which 142 patients with SSc-ILD received oral MMF for two years or oral CYC for 1 year followed by placebo for 1 year, improvements in FVC per cent predicted, dyspnea and skin thickness was observed at 2 years in both groups, with no significant difference between the groups, but with fewer treatment discontinuations due to adverse events in patients treated with MMF than CYC [Tashkin 2016]. The latest treatment guidelines for SSc issued by the European League Against Rheumatism Collaborative Initiative (EULAR) and the EULAR Scleroderma Trials and Research Group (EUSTAR) recommend tailored CYC therapy for the treatment of SSc-ILD, particularly for patients with progressive disease [Kowal-Bielecka 2017]. These guidelines also recommend that autologous hematopoietic stem cell transplantation (HSCT) should be considered for selected patients with rapidly progressive SSc at risk of organ failure, with careful evaluation of the risk-benefit profile for individual patients. HSCT has shown considerable benefits in selected patients with SSc, but is associated with significant treatment-related mortality [Eyraud 2017].

**Pathogenesis of SSc and SSc-ILD**

The pathogenesis of SSc is complex and incompletely understood. The clinical manifestations of SSc are believed to result from distinct but interdependent processes: a) vascular damage involving microvascular endothelial cells leading to fibroproliferative vasculopathy and capillary rarefication, perivascular inflammation and autoimmune activation, b) innate and adaptive immune system abnormalities leading to production of autoantibodies, cell-mediated autoimmunity and the release of pro-fibrotic mediators and ultimately c) activation of fibroblasts to myofibroblasts, resulting in excessive deposition of extracellular matrix (ECM) in skin, lung, blood vessels and internal organs [Denton 2006; Pattanaik 2015].

Damage to vascular endothelial cells, which may result from physical trauma, ischemia reperfusion injury, infectious agents, cytotoxic T cells, autoantibodies or oxidative stress, evokes the release of chemokines, endothelins, platelet-derived growth factor and vascular endothelial growth factor [Distler 2002; Distler 2004]. These alter endothelial permeability and promote the recruitment and proliferation of leukocytes. Under normal conditions, these factors and cells would orchestrate the healing process, stimulating tissue repair and scar resolution. However, in SSc, repeated vascular injury and a failure to resolve the

inflammatory response and repair the endothelium evoke adaptive and innate immunologic mechanisms, including the accumulation of macrophages and neutrophils, which enhance the recruitment of lymphocytes to sites of injury. The role of endothelial apoptosis in the pathogenesis of SSc is not clear. Apoptosis of endothelial cells may contribute to tissue injury when they are engulfed by macrophages and immature dendritic cells, which then present cellular antigens to T cells [Albert 2001]. Apoptotic endothelial cells can also activate the complement and coagulant pathway, leading to vasculopathy [Tsuji 1994; Greeno 1996]. The involvement of monocytes/macrophages in the development and progression of SSc is also debated. Classically activated macrophages of the M1 type and alternatively activated macrophages of the M2 type belong to several subgroups stimulated by mediators like IFNγ, TNF, IL-4, IL-13, IL-10 and M-CSF. Both M1 and more prominently M2 signatures have been described in the blood, skin and lung of patients with SSc, but their relevance remains to be defined [Stifano 2016].

Plasma cells secrete highly specific autoantibodies against host cell antigens and can exacerbate tissue injury. Endothelial-derived chemokines and growth factors recruit and activate mesenchymal progenitor cells and resident fibroblasts. Profibrotic factors secreted by activated T cells promote fibroblast activation and the synthesis and secretion of ECM. Differentiation of fibroblasts into contractile myofibroblasts expressing alpha smooth muscle actin amplifies the pathologic processes. Persistent production and deposition of ECM components, notably the fibrillar collagens type I and III, within connective tissues leads to fibrosis, tissue contraction and scarring. This inflammation phase is characterized by T-cell activation and the development of T-cells with predominantly type 2 T-helper-cell profibrotic cytokine profiles (IL-4, IL-5, IL-13). Other T-cell subsets and B cells are also present in lesions and exhibit intrinsic abnormalities in their phenotype and function. Inflammation is critical to the activation, recruitment and expansion of mesenchymal cell populations, including fibroblasts, pericytes and circulating progenitor cells, which contribute to the scarring process.

SSc-ILD shows similarities to IPF in the pathophysiology of the underlying fibrotic cascade. While the initiating and amplifying events are described to be different in SSc-ILD and IPF [Herzog 2014], both culminate in fibroblast activation, migration, proliferation and myofibroblast accumulation with excessive ECM deposition; this represents a common final pathway of lung fibrosis [Bagnato 2015].

**Mechanism of action of nintedanib in SSc and SSc-ILD**

Nintedanib is a small molecule tyrosine kinase inhibitor (TKI) that binds competitively to the adenosine triphosphate (ATP) binding pocket of kinases, blocking their downstream

signalling [Wollin 2015]. Nintedanib targets the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3 [Hilberg 2008; Wollin 2014]. In addition, nintedanib inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn), Src (proto-oncogene tyrosine-protein kinase src) kinases [Hillberg 2008] and the colony-stimulating factor 1 receptor (CSF1R) [Tandon 2017; Hilberg 2018]. Several of these kinase targets have been linked to pathogenic processes in lung fibrosis [Inoue 1996; Bonner 2004; Beyer 2013]. Recently, additional potential kinase targets were described for nintedanib [Hilberg 2018], but their relevance for its anti-fibrotic activity is unknown.

Nintedanib was originally developed to be a treatment for non-small cell lung cancer by blocking neo-angiogenesis and with it, tumor growth. Pre-clinical pharmacodynamic exploration revealed that nintedanib attenuates the proliferation of three cell types contributing to angiogenesis: endothelial cells, pericytes, and smooth muscle cells [Hillberg 2008]. Later, nintedanib was developed as a treatment for IPF, which shows several similarities in pathogenic pathways to cancer [Vancheri 2015]. Based on clinical trial data showing that nintedanib reduces the progression of IPF by slowing decline in lung function [Richeldi 2011; Richeldi 2014], nintedanib has been approved for the treatment of IPF in many countries worldwide.

The mode of action of nintedanib in lung fibrosis has been characterized based on *in vitro* studies and *in vivo* models. Nintedanib inhibits the proliferation, migration and contraction of lung fibroblasts from patients with IPF [Wollin 2015], as well as attenuating the differentiation and migration of pro-fibrotic fibrocytes [Sato 2017] and the transformation of lung fibroblasts to myofibroblasts [Wollin 2014]. Recently, nintedanib was also shown to restore the elastic modulus of fibrotic matrices to reverse the myofibroblastic phenotype of pericytes [Sava 2017]. Nintedanib has demonstrated anti-fibrotic and anti-inflammatory activity in animal models of lung fibrosis created using a variety of triggers [Wollin 2014; Wollin 2015; Ackermann 2017]. In these models, nintedanib attenuated the accumulation of lymphocytes in bronchoalveolar lavage fluid; reduced levels of interleukin-1β, the chemokine CXCL1/KC, and the tissue inhibitor of metalloproteinases-1; blocked expression of fibrosis-related marker genes such as TGFβ1 and procollagen 1; reduced histology scores of inflammation, granuloma formation and fibrosis in the lungs; reduced lung tissue density and the collagen content of lung tissue; and improved static lung compliance [Wollin 2014; Wollin 2015; Ackermann 2017]. In a mouse model of bleomycin-induced lung fibrosis, nintedanib also attenuated vascular proliferation, resulting in normalization of the distorted microvascular architecture [Ackermann 2017].

Recent *in vivo* investigations have revealed antifibrotic and anti-inflammatory activities of nintedanib in animal models of aspects of SSc. In bleomycin-induced skin fibrosis, graft versus host disease-induced skin fibrosis, tight skin (fibrillin1 transgenic), and Fra-2 mouse models of SSc, nintedanib reduced myofibroblast accumulation and ECM deposition in skin and lung, attenuated skin and lung fibrosis, and reduced dermal thickening [Huang 2016; Huang 2017]. In Fra-2 +/- transgenic mice, nintedanib also attenuated pulmonary vascular remodeling by reducing the number of vascular smooth muscle cells, pulmonary vascular wall thickness and occluded pulmonary vessels and by inhibiting microvascular endothelial cell apoptosis, and reduced the extent of fibrosis, perivascular inflammation and endothelial cells apoptosis in the heart [Huang 2017]. In *in vitro* studies, nintedanib has been shown to block the release of pro-fibrotic mediators from human peripheral blood monocytic cells and T cells [Wollin 2017] and reduce the M2 polarization of human macrophages incubated with macrophage colony-stimulating factor, interleukin IL-4 and IL-13 [Huang 2017; Tandon 2017]. In experiments in dermal fibroblasts from patients with SSc, nintedanib inhibited fibroblast migration and proliferation, reduced the expression of ECM markers collagen 1a1, 1a2, and fibronectin, and attenuated transformation of fibroblasts to myofibroblasts as detected by reductions in αSMA and stress fibers [Huang 2016]. An overview of the pre-clinical exploration of nintedanib in dermal fibroblasts from patients with SSc and in *in vivo* models of SSc/SSc-ILD is presented in Tables 1 and 2.

The comparable efficacy of nintedanib in animal models of lung fibrosis and SSc suggests that the effective dose may be comparable in patients with IPF and SSc. Nintedanib effectively inhibited fundamental processes of skin fibrosis (*i.e.,* the proliferation and migration of dermal fibroblasts) at concentrations of 100 nM, which are close to the exposure levels achieved in humans (59 - 74 nmol/L) after steady state oral dosing of nintedanib 150 mg twice daily in patients with IPF [Mross 2010; Eisen 2013].

**Clinical investigation of nintedanib in SSc-ILD**

The efficacy and safety of nintedanib in patients with SSc-ILD are being assessed in the randomized placebo-controlled SENSCIS® trial (ClinicalTrials.gov NCT02597933; EudraCT 2015-000392-28) [Distler 2017]. Over 520 patients aged ≥18 years with onset of SSc (first non-Raynaud symptom) ≤7 years before screening, ILD (≥10% fibrosis of the lungs on HRCT), FVC ≥40% predicted and diffusion capacity of the lung for carbon monoxide 30–89% predicted have been enrolled. Patients receiving low-dose prednisone and/or stable background therapy with MMF or methotrexate have been included in the trial, to reflect clinical practice. Patients have been randomized to receive nintedanib 150 mg twice daily or placebo. Randomized patients were stratified by the presence of anti-Scl-70/anti-topoisomerase I antibody, which has been associated with accelerated progression of ILD

[Assassi 2010]. The primary endpoint is the annual rate of decline in FVC (mL/year) assessed over 52 weeks. Key secondary endpoints are absolute changes from baseline in the modified Rodnan Skin Score (a measure of skin thickening in patients with SSc) and in the St George's Respiratory Questionnaire total score (a measure of health-related quality of life) at week 52. The SENSCIS® trial is due to be completed near the end of 2018.

## Conclusions

There is a high unmet need for effective treatments for SSc-ILD. Nintedanib is an approved treatment for IPF, which shows clinical and mechanistic similarities to SSc-ILD. Nintedanib interferes at multiple critical steps in the pathobiology of SSc/SSc-ILD and has demonstrated anti-inflammatory and anti-fibrotic activities and attenuated vascular remodeling in several models of SSc/SSc-ILD, providing a strong rationale for its investigation as a treatment for SSc-ILD. The efficacy and safety of nintedanib in patients with SSc-ILD are currently being investigated in the Phase III SENSCIS® trial.

## Acknowledgements

Editorial assistance, supported financially by Boehringer Ingelheim, was provided by Wendy Morris of FleishmanHillard Fishburn, London, UK during the preparation of this article. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

**Tables and Figures**

Error! Reference source not found. **Exploration of Nintedanib in Dermal Fibroblasts from Patients with SSc** [Huang 2016]

| **Model system/characteristics** | **Effects of nintedanib** |
|---|---|
| TGFβ- and PDGF-induced ECM components and markers of fibroblast to myofibroblast transformation | Collagen 1a1, 1a2, fibronectin, αSMA mRNA ↓<br><br>Collagen, stress fibers and TGFβ signaling ↓ |
| TGFβ- and PDGF-induced proliferation and migration of fibroblasts | TGFβ- and PDGF-induced proliferation ↓<br><br>TGFβ- and PDGF-induced migration ↓ |

ECM, extracellular matrix; PDGF, platelet-derived growth factor; αSMA, alpha smooth muscle actin; TGFβ, transforming growth factor beta.

Error! Reference source not found.**Exploration of Nintedanib in Mouse Models of SSc /SSc-ILD** [Huang 2016; Huang 2017]

| **Model system** | **Model characteristics** | **Treatment regimen** | **Effects of nintedanib** |
|---|---|---|---|
| Bleomycin-induced skin fibrosis | Skin damage-induced/ inflammation-induced fibrosis | Preventive (weeks 0-3) and therapeutic (weeks 3-6) | Skin:<br>Myofibroblast count ↓<br>Dermal thickness ↓<br>Hydroxyproline ↓ |
| Graft versus host disease-induced skin fibrosis | Resembles aspects of early inflammatory stage of SSc | Therapeutic (weeks 4-8) | Skin:<br>Myofibroblast count ↓<br>Dermal thickness ↓<br>Hydroxyproline ↓ |
| Tight skin (fibrillin1 transgenic) | Resembles aspects of later stage of SSc with less inflammation, but early autoantibody production and massive fibrosis | Therapeutic (weeks 5–10) | Skin:<br>Myofibroblast count ↓<br>Hypodermal thickness ↓<br>Hydroxyproline ↓ |
| Fra-2 (AP-1 family transcription factor +/-) | Resembles aspects of skin and lung fibrosis including microvascular disease and pulmonary hypertension with typical vascular lesions | Therapeutic (weeks 9-16) | Skin:<br>Myofibroblasts count ↓<br>Dermal thickness ↓<br>Hydroxyproline ↓<br>MVEC apoptosis ↓<br>Capillary loss ↓<br>M2 macrophages ↓<br><br>Lung:<br>Myofibroblast count ↓<br>ECM ↓<br>Vessel wall thickness ↓<br>Occluded vessels ↓<br>VSMC ↓<br>MVEC apoptosis ↓<br><br>Heart:<br>Extent of fibrosis ↓<br>Perivascular inflammation ↓<br>Endothelial cells apoptosis ↓ |

ECM, extracellular matrix; VSMC; lung vascular smooth muscle cells; MVEC, dermal microvascular endothelial cells.

**Figure 1. Effects of Nintedanib on Pathogenic Mechanisms with Potential Relevance in SSc**

This figure depicts pathogenic mechanisms of SSc that have been shown to be targeted by nintedanib in experiments on human cells or in animal models resembling aspects of SSc and lung fibrosis.

Nintedanib potently targets fibroblast growth factor receptors (FGFR), platelet-derived growth factor receptors (PDGFR), vascular endothelial growth factor receptor (VEGFR), lymphocyte-specific tyrosine-protein kinase (Lck) and colony-stimulating factor 1 receptor (CSF1R). Nintedanib also exerts vascular effects, *i.e*. inhibits the proliferation of endothelial cells and pericytes. Nintedanib reduces the recruitment of lymphocytes to the lung. Nintedanib inhibits the differentiation and migration of fibrocytes and the migration, proliferation and contraction of fibroblasts. By reducing the number of fibroblasts and their transformation to myofibroblasts, the secretion of extracellular matrix (ECM) is reduced. Further, nintedanib blocks the differentiation of alternatively activated macrophages and the release of pro-fibrotic mediators from T cells involved in the initiation of fibrosis.

**References**


Ackermann M, Kim YO, Wagner WL, et al. Effects of nintedanib on the microvascular architecture in a lung fibrosis model. Angiogenesis 2017;20:359-372.

Adler S, Huscher D, Siegert E, et al. Systemic sclerosis associated interstitial lung disease - individualized immunosuppressive therapy and course of lung function: results of the EUSTAR group. Arthritis Res Ther 2018;20:17.

Albert ML, Jegathesan M, Darnell RB. Dendritic cell maturation is required for the cross-tolerization of CD8+ T cells. Nat Immunol 2001;2:1010-1017.

Allanore Y, Simms R, Distler O, et al. Systemic sclerosis. Nat Rev Dis Primers 2015;1:15002.

Assassi S, Sharif R, Lasky RE, et al. Predictors of interstitial lung disease in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. Arthritis Res Ther 2010;12:R166.

Beyer C, Distler JH. Tyrosine kinase signaling in fibrotic disorders: Translation of basic research to human disease. Biochim Biophys Acta 2013;1832:897-904.

Bagnato G, Harari S. Cellular interactions in the pathogenesis of interstitial lung diseases. Eur Respir Rev 2015;24:102-114.

Baron M, Sutton E, Hudson M, et al. The relationship of dyspnoea to function and quality of life in systemic sclerosis. Ann Rheum Dis 2008;67:644-50.

Bonner JC. Regulation of PDGF and its receptors in fibrotic diseases. Cytokine Growth Factor Rev 2004;15:255-73.

Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med 2016;194:265-75.

Denton CP, Black CM, Abraham DJ. Mechanisms and consequences of fibrosis in systemic sclerosis. Nat Clin Pract Rheumatol 2006;2:134-144.

Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685-1699.

Distler O, Del Rosso A, Giacomelli R, et al. Angiogenic and angiostatic factors in systemic sclerosis: increased levels of vascular endothelial growth factor are a feature of the earliest disease stages and are associated with the absence of fingertip ulcers. Arthritis Res 2002;4:R11.

Distler O, Distler JH, Scheid A, et al. Uncontrolled expression of vascular endothelial growth factor and its receptors leads to insufficient skin angiogenesis in patients with systemic sclerosis. Circ Res 2004;95:109-116.

Distler O, Brown KK, Distler JHW, et al. Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS). Clin Exp Rheumatol 2017;35:75-81.

Eisen T, Shparyk Y, Macleod N, et al. Effect of small angiokinase inhibitor nintedanib (BIBF 1120) on QT interval in patients with previously untreated, advanced renal cell cancer in an open-label, phase II study. Invest New Drugs 2013;31:1283-1293.

Eyraud A, Scouppe L, Barnetche T, et al. Efficacy and safety of autologous haematopoietic stem cell transplantation in systemic sclerosis: A systematic review of literature. Br J Dermatol 2017; doi: 10.1111/bjd.15993; epub ahead of print.

Greeno EW, Bach RR, Moldow CF. Apoptosis is associated with increased cell surface tissue factor procoagulant activity. Lab Invest 1996;75:281-289.

Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Review: interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? Arthritis Rheumatol 2014;66:1967-1978.

Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68:4774-4782.

Hilberg F, Tontsch-Grunt U, Baum A, et al. Triple angiokinase inhibitor nintedanib directly inhibits tumor cell growth and induces tumor shrinkage via blocking oncogenic receptor tyrosine kinases. J Pharmacol Exp Ther 2018;364:494-503.

Huang J, Beyer C, Palumbo-Zerr K, et al. Nintedanib inhibits fibroblast activation and ameliorates fibrosis in preclinical models of systemic sclerosis. Ann Rheum Dis 2016;75:883-890.

Huang J, Maier C, Zhang Y, et al. Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the Fra2 mouse model of systemic sclerosis. Ann Rheum Dis 2017;76:1941-1948.

Hudson M, Thomas BD, Steele R, et al. Clinical correlates of quality of life in systemic sclerosis measured with the World Health Organization Disability Assessment Schedule II. Arthritis Rheum 2008;59:279-284.

Inoue Y, King TE Jr, Tinkle SS, et al. Human mast cell basic fibroblast growth factor in pulmonary fibrotic disorders. Am J Pathol. 1996;149:2037-54.

Jaeger VK, Wirz EG, Allanore Y, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. PLoS One 2016;11(10):e0163894.

Khanna D, Tseng CH, Farmani N, et al. Clinical course of lung physiology in patients with scleroderma and interstitial lung disease: analysis of the Scleroderma Lung Study placebo group. Arthritis Rheum 2011;63(10):3078-85.

Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327-1339.

Matucci-Cerinic M, Krieg T, Guillevin L, et al. Elucidating the burden of recurrent and chronic digital ulcers in systemic sclerosis: long-term results from the DUO Registry. Ann Rheum Dis 2016;75:1770-1776.

Mross K, Stefanic M, Gmehling D, et al. Phase I study of the angiogenesis inhibitor BIBF 1120 in patients with advanced solid tumors. Clin Cancer Res 2010;16:311-319.

Pattanaik D, Brown M, Postlethwaite BC, Postlethwaite AE. Pathogenesis of systemic sclerosis. Front Immunol 2015;6:272.

Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;365:1079-1087.

Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-2082.

Rubio-Rivas M, Royo C, Simeón CP, et al. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum 2014;44:208-219.

Sato S, Shinohara S, Hayashi S, et al. Anti-fibrotic efficacy of nintedanib in pulmonary fibrosis via the inhibition of fibrocyte activity. Respir Res 2017;18:172.

Sava P, Ramanathan A, Dobronyi A, et al. Human pericytes adopt myofibroblast properties in the microenvironment of the IPF lung. JCI Insight. 2017;2(24):e96352.

Siegert E, Huscher D, Müller-Ladner U, et al. Current use of off-label therapies in systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol. 2016;68(suppl 10). Abstract presented at ACR 2016.

Stifano G, Christmann RB. Macrophage involvement in systemic sclerosis: do we need more evidence? Curr Rheumatol Rep 2016;18:2.

Tandon K, Herrmann F, Ayaub E, et al. Nintedanib attenuates the polarization of profibrotic macrophages through the inhibition of tyrosine phosphorylation on CSF1 receptor. Am J Respir Crit Care Med 2017;195:A2397.

Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655-2666.

Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708-719.

Tomiyama F, Watanabe R, Ishii T, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. Tohoku J Exp Med 2016;239:297-30.

Tsuji S, Kaji K, Nagasawa S. Activation of the alternative pathway of human complement by apoptotic human umbilical vein endothelial cells. J Biochem 1994;116:794-800.

Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809-1815.

Vancheri C. Idiopathic pulmonary fibrosis and cancer: do they really look similar? BMC Med 2015;13:220.

Walker KM, Pope J; participating members of the Scleroderma Clinical Trials Consortium (SCTC); Canadian Scleroderma Research Group (CSRG). Treatment of systemic sclerosis complications: what to use when first-line treatment fails--a consensus of systemic sclerosis experts. Semin Arthritis Rheum 2012;42:42-55.

Wollin L, Maillet I, Quesniaux V, et al. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther 2014;349:209-220.

Wollin L, Wex E, Pautsch A, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J 2015;45:1434-1445.

Wollin L, Ostermann A, Williams C. Nintedanib inhibits pro-fibrotic mediators with relevance in connective tissue disease-associated interstitial lung diseases. Am J Respir Crit Care Med 2017;195:A2450.