Contemporary Clinical Trials Communications 23 (2021) 100832

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Design of phase 2 study of TAS-115, a novel oral multi-kinase inhibitor, in patients with idiopathic pulmonary fibrosis

Yasuhiko Nishioka [a,*], Sakae Homma [b], Takahito Okubo [c], Arata Azuma [d]

[a] Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan
[b] Department of Advanced and Integrated Interstitial Lung Diseases Research, School of Medicine, Toho University, Tokyo, Japan
[c] Early Clinical Development, Oncology, Clinical Development Division, Taiho Pharmaceutical Co., Ltd, Tokyo, Japan
[d] Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

ARTICLE INFO

Keywords:
Clinical trial
Forced vital capacity
Idiopathic pulmonary fibrosis
Multi-kinase inhibitor
Phase 2

ABSTRACT

Background: TAS-115, a novel multi-kinase inhibitor, demonstrated antifibrotic effects *in vitro* and *in vivo*.
Methods: This is an open-label, intra-patient comparison, exploratory phase 2 study of TAS-115 to evaluate the efficacy and safety in idiopathic pulmonary fibrosis (IPF) patients when orally administered at 200 mg once daily on a 5-day on and 2-day off regimen for 13 weeks. This study consists of three cohorts: previously treated with pirfenidone (Cohort P, n = 20), with nintedanib (Cohort N, n = 20), and treatment naïve (Cohort U, n = 10). Male or female patients aged ≥40 to <80 years who were diagnosed with IPF in the preceding five years and having a percent predicted forced vital capacity (%FVC) decline of ≥5% within the previous 6 months were enrolled in this study. The primary endpoint is change in the slope of %FVC decline at Week 13 from baseline. Key secondary endpoints are safety, change in FVC from baseline, proportion of the %FVC responders and change in percent predicted diffusing capacity of the lung carbon monoxide from baseline, which are assessed at Weeks 6, 13 and 26.
Results: Enrollment of 45 patients was completed in July 2019. Results will be reported in 2021.
Discussion: This trial is intended to demonstrate the clinical efficacy of TAS-115 in IPF patients who have not responded to pirfenidone or nintedanib, as well as in those who are pirfenidone/nintedanib treatment naïve. The safety and tolerability in this population will be assessed.
Trial registration: JapicCTI-183898.

1. Introduction

Idiopathic pulmonary fibrosis (IPF), a type of idiopathic interstitial pneumonia (IIP), is the most common and lethal diffuse fibrosing lung disease. It is characterized by a chronic clinical course with highly progressive fibrosing of unknown cause [1–3]. The disease is more common among males, particularly, among those with a history of smoking [4,5] and is a disease of older adults who are often aged 60–70 years at the time of diagnosis [6]. In Europe and the United States (US), the estimated morbidity and prevalence per 0.1 million population were reported to be 0.22 to 17.4 and 1.25 to 63, respectively [7]. Median survival from the time IPF diagnosis is two to four years [4,6], and less than six months in patients who experience an acute exacerbation [3,4]. Maintaining respiratory function by pharmacological intervention during the chronic phase is very important [8]. The molecular mechanisms involved in the progression of IPF are not fully understood, however, alveolar epithelial type II cells and fibroblasts are thought to be the main mediators of the process [6]. Currently, pirfenidone and nintedanib have been used for the treatment of IPF patients [9–11]. Nintedanib is an inhibitor of multiple tyrosine kinases, including receptors for platelet-derived growth factor (PDGF), fibroblast growth factor, and vascular endothelial growth factor [12]. Evidence suggests that pirfenidone inhibits fibroblast proliferation and collagen synthesis and reduces cellular and histological markers of fibrosis through regulation of the activity of transforming growth factor (TGF) β and tumor necrosis factor (TNF) α [13]. However, these antifibrotic drugs are not sufficiently effective: 45% of the patients treated with pirfenidone had an annual rate of ≥5% forced vital capacity (FVC) decline, and approximately 75% of the patients treated with nintedanib experienced

* Corresponding author. Ph.D. Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University 3-18-15, Kuramoto-cho, Tokushima, 770-8503, Japan.
E-mail address: yasuhiko@tokushima-u.ac.jp (Y. Nishioka).

https://doi.org/10.1016/j.conctc.2021.100832
Received 3 December 2020; Received in revised form 5 August 2021; Accepted 17 August 2021
Available online 18 August 2021
2451-8654/© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Abbreviations

AE	adverse event
DLco	diffusing capacity of the lung carbon monoxide
EOT	end of treatment
FAS	full analysis set
FEV1	forced expiratory volume in one
FMS	colony stimulating factor-1 receptor
FVC	forced vital capacity
%FVC	percent predicted forced vital capacity
HGFR	hepatocyte growth factor receptor
HRCT	high-resolution computed tomography
IC	informed consent
IIP	idiopathic interstitial pneumonia
IPF	idiopathic pulmonary fibrosis
MedDRA	Medical Dictionary for Regulatory Activities
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PPS	per protocol set
SpO_2	oxygen saturation of peripheral artery
TGF	transforming growth factor
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TRAE	treatment-related adverse events
VC	vital capacity
VEGFR	vascular endothelial growth factor receptor
US	United States
UIP	Usual interstitial pneumonia

FVC decline [14,15]. Furthermore, adverse drug reactions such as gastrointestinal toxicities reduce patient adherence to these drugs [16,17]. In the international guideline on the treatment of IPF, while pirfenidone and nintedanib are recommended, the recommendation is conditional due to only moderate confidence in effect estimates [18]. Therefore, drugs that are both safe and more potent are needed.

TAS-115 is a novel oral multi-kinase inhibitor originally developed to treat various types of cancer. TAS-115 inhibits the autophosphorylation of a number of receptors that are known to be involved in the pathogenic process of IPF. These include platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), hepatocyte growth factor receptor (HGFR), colony stimulating factor-1 receptor (FMS), and other receptors that are competitively inhibited by adenosine triphosphate [19]. TAS-115 showed antifibrotic effects that were comparable or superior to those of nintedanib, *in vitro* and in an animal model of IPF [20]. A phase 1 clinical trial of TAS-115 in cancer patients [21] reported that most common treatment-related adverse events (TRAE) were laboratory abnormalities, gastrointestinal symptoms, general disorders and skin disorders, indicating that the profile was different from the profiles of pirfenidone and nintedanib. We planned this exploratory phase 2 clinical trial of TAS-115 to evaluate the therapeutic effect and safety in IPF patients.

2. Materials and methods

2.1. Trial organization and ethical matters

The study was designed and conducted by the sponsor, Taiho Pharmaceutical Co., Ltd., Tokyo, Japan in collaboration with the principal investigators. The sponsor monitored study conduct, collected the data, and performed the statistical analyses. The study was conducted at ten sites in Japan from April 2018 to June 2020. The study protocol and informed consent form were approved by the institutional review board at each participating study site. All patients gave written informed consent before initiation of any study-specific procedures. The study was conducted in accordance with the ethical principles originating in or derived from the Declaration of Helsinki, Good Clinical Practice guidelines.

2.2. Study design

This study is an open-label, non-randomized, multicenter, exploratory phase 2 study to evaluate the efficacy and safety of TAS-115 in IPF patients. The study design is shown in Fig. 1. TAS-115 was administered for 13 weeks in IPF patients and the treatment could be extended for up to 26 weeks (additional administration period of 13 weeks). The study consists of three cohorts: patients previously treated with pirfenidone (Cohort P), patients previously treated with nintedanib (Cohort N), and pirfenidone/nintedanib treatment naïve patients (Cohort U). After completion of 13-week treatment, a 28-day follow-up was performed.

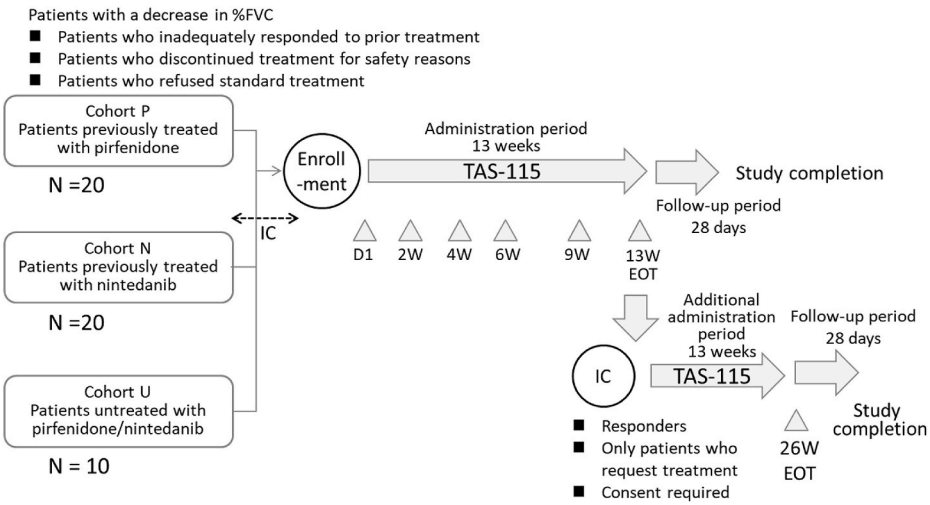

Fig. 1. Study design. IC, informed consent; EOT, end of treatment; %FVC, percent predicted forced vital capacity.

2.3. Patients

Male or female patients aged ≥40 to <80 years who were diagnosed with IPF in accordance with the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association Guideline [1] in the preceding 5 years were enrolled into the study. High-resolution computed tomography (HRCT) had to show a pattern of usual interstitial pneumonia (UIP) to provide a diagnosis of IPF. If HRCT could not provide a definitive diagnosis, a diagnosis was made based on HRCT and surgical lung biopsy. Key inclusion and exclusion criteria are shown in Table 1.

2.4. Treatment

TAS-115 was orally administered at 200 mg once daily at bedtime. Patients were advised to finish meals at least 2 h before administration. The dosing regimen was five consecutive days followed by two days of rest per week (5-day on and 2-day off regimen), and this cycle was repeated for 13 weeks. After completion of the 13-week treatment period, patients could enter into a 13-week extension treatment phase provided the percent predicted forced vital capacity (%FVC) change rate (%FVC decline slope) at Week 13 was lower than that at baseline; patients did not meet the criteria for treatment discontinuation; the investigator considered that additional administration was feasible; and the patient was willing to continue treatment and provide written consent. Administration with TAS-115 was discontinued in the following cases: worsening of symptoms; lung transplantation; an adverse event (AE) that made it impossible to continue administration; non-adherence >28 consecutive days; a critical protocol deviation; or request for treatment termination by either the patient or investigator. Treatment with TAS-115 was interrupted if the following AEs occurred: neutrophil count decreased <500/mm^3, platelet count decreased <5 × 10^4/mm^3, and total bilirubin >2-fold of the upper limit of the institutional reference range. After resumption of administration, a 5-day on and 2-day off regimen was followed. A single treatment interruption period could not exceed 28 days. The dosage of TAS-115 had to be reduced in the event of severe TRAEs that do not remit or resolve after symptomatic treatment.

Table 1
Key inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
· Patients whose age at the time of informed consent is ≥ 40 to <80 years · % FVC ≥50% · % DLco ≥30% · Patients who meet any of the following; ✓ Monotherapy with either pirfenidone or nintedanib was continued for ≥3 months as IPF treatment, and %FVC decline ≥5% within the previous six months. ✓ Monotherapy with pirfenidone or nintedanib was discontinued due to safety concerns, and %FVC decline was identified during the previous three months. ✓ The patient has been treated with neither pirfenidone nor nintedanib, does not request treatment with these drugs, and %FVC decline ≥5% during the previous six months.	· History of combination therapy with pirfenidone and nintedanib · Patients who received the following treatment during the specified period before enrollment in this study; ✓ Treatment with either pirfenidone or nintedanib within one week before enrollment ✓ N-acetylcysteine, systemic prednisolone (>10 mg/day), or comparable steroids, or treatment with azathioprine, cyclosporine, or cyclophosphamide within eight weeks before enrollment ✓ Surgery within four weeks before enrollment ✓ Treatment with other investigational drugs within eight weeks before enrollment · Airflow obstruction (FEV1/FVC <0.7 within 28 days before enrollment) · Comorbid lung cancer · Severe pulmonary hypertension · Acute exacerbation of IPF within three months before enrollment

DLco, diffusing capacity of the lung carbon monoxide; FEV1/FVC, percent forced expiratory volume in 1 s; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

In the case of mild taste disturbance, moderate or severe fatigue, or skin eruption, dose reduction to 100 mg/day could be considered.

2.5. Outcome measures

The primary endpoint of this study was the difference in %FVC change rate (%FVC decline slope) at Week 13 from baseline (Fig. 2). The %FVC change rate at baseline was calculated from (%FVC at baseline – %FVC at the time when the inclusion criteria were confirmed)/observation period. The %FVC change rate at Week 13 was calculated from (%FVC at Week 13 − %FVC at Day 1)/observation period (13 weeks). The %FVC was calculated from measured FVC/predicted FVC × 100. The predicted FVC was calculated from the prediction formula for spirometry reference values according to the lambda-mu-sigma method reported by the Clinical Pulmonary Functions Committee of the Japanese Respiratory Society in 2014 [22].

Key secondary endpoints were (1) difference in %FVC change rate at Week 6 from baseline, (2) difference in FVC at Week 6 and 13 from baseline, (3) proportion of %FVC responders at Weeks 6 and 13. Responders were defined as patients with an absolute reduction of ≤5% and patients with an absolute reduction of ≤10%, (4) difference in vital capacity (VC) at Weeks 6 and 13 from baseline, (5) difference in % diffusing capacity of the lung carbon monoxide (DLco) at Weeks 6 and 13 from baseline, (6) difference in %FVC and %DLco, and proportion of %FVC responders at Week 26 from baseline, (7) safety. For safety assessment, medical interview, blood biochemistry tests, urinalysis, and AE observation was performed during the study including the extension treatment period. Vital signs, body weight, and 12-lead electrocardiogram findings were also assessed.

2.6. Target sample size

The planned maximum target sample size was 50 (20 in Cohort P, 20 in Cohort N, and 10 in Cohort U). At least 20 of these patients had to have been inadequate responders to prior treatment.

There was no statistical rationale for the size of target sample employed in the study. The objective of the study was to exploratory investigate changes in %FVC after 13-week administration of TAS-115 in IPF patients. Therefore, while the target sample size could not have been identified in advance, we assumed that information on the objective would be obtained in up to 50 patients.

2.7. Statistical analysis

Statistical analyses were carried out at the following three time points. (1) The first analysis was performed after the completion of the lung function test at Week 13 in patients enrolled within four months after the enrollment of the first patient. (2) At the primary evaluation. Statistical analyses were performed at the time all patients finished treatment in Week 13. (3) At the completion of the study. Analyses were performed at study termination in all patients.

Efficacy analyses were performed in the full analysis set (FAS); patients who satisfied the inclusion criteria without meeting the exclusion criteria and were evaluated for efficacy at least once after TAS-115 administration, and per protocol set (PPS); patients in the FAS who underwent the specified lung function test at Week 13 and had a treatment adherence of ≥60% until Week 13. Primary analysis for the primary endpoint was performed by cohort in the PPS. Summary statistics of difference in percent reduction in %FVC at Week 13 from baseline were calculated. Secondary analyses were conducted in FAS. Analyses of oxygen saturation of peripheral artery (SpO_2) and arterial blood gas test were performed by cohort in the PPS and FAS, and analysis of presence or absence of acute exacerbation was performed by cohort. The percentage of patients with acute exacerbation and the 95% confidence interval, and its median acute exacerbation time (range) and the 95% confidence interval were calculated. Safety was assessed in all treated

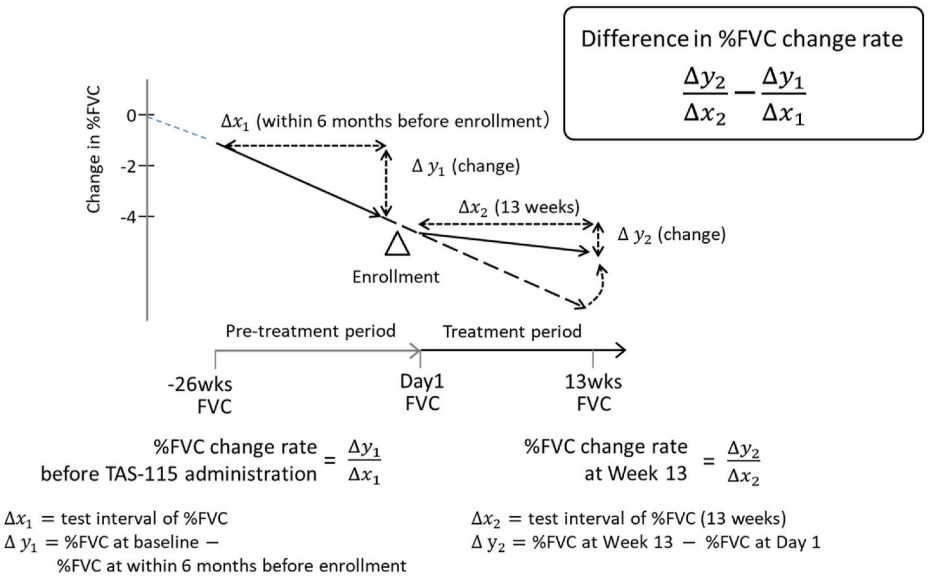

Fig. 2. Change in forced vital capacity (FVC).

patients who received at least one dose of TAS-115 by cohort. AEs that occurred after TAS-115 administration were classified as treatment-emergent AEs (TEAEs). TRAEs were defined as TEAEs related to TAS-115.

3. Discussion

3.1. Rationale for study design, population, and treatment

TAS-115, a novel oral multi-kinase inhibitor initially developed as an anticancer drug, inhibits proliferation and migration of fibroblasts by its potent PDGFR and VEGFR inhibitory effects and suppresses FMS-derived fibrillization through macrophages activation. The safety profile of TAS-115 is different from that of multi-kinase inhibitor nintedanib because of the shorter half-life in the blood [21]. It is anticipated that TAS-115 will prove to be a promising candidate drug for the treatment of IPF patients with chronic progressive disease, particularly non-responders and/or patients unable to tolerate pirfenidone or nintedanib, since these two drugs have demonstrated only moderate efficacy and the recommendation is a conditional one in the international guideline on treatment of IPF [18]. Therefore, we designed this open-label study to explore the efficacy and safety of TAS-115 in IPF patients.

The dose of TAS-115 in this study is 200 mg/day, which is considered to be the maximum dose that can be administered in long-term continuous treatment without safety concerns based on the phase 1 study in patients with solid tumors [21]. This is because this study is not intended to explore the dose response and we designed to evaluate whether TAS-115 is effective in IPF patients over an extended period.

3.2. Rationale for endpoints

We decided to use %FVC as a primary endpoint in this early stage clinical trial because it was reported [23–25] that change in FVC over time was associated with life prognosis and FVC or %FVC has been accepted to be an adequate primary endpoint even in phase 3 studies. Our study does not have a comparator; therefore, the efficacy was assessed by intra-patient difference in %FVC change rate (%FVC decline slope) at Week 13 from baseline. The %FVC change rate (%FVC decline slope) at each time assessment was calculated based on %FVC change during a certain observation period. %FVC change rate (%FVC decline slope) at baseline was assessed based on medical records, in which the observation period before study commencement is variable. If the %FVC change rate at Week 13 was higher than the estimated %FVC based on % FVC at six months before administration, the difference is regarded as positive and suggests slowed disease progression due to a reduction in % FVC decline. If the %FVC change rate at Week 13 is lower than estimated %FVC at six months before administration, the difference is regarded as negative and suggests accelerated disease deterioration due to increasing %FVC decline. A slope evaluation using a regression line was performed, since measurement bias in %FVC may be involved in this assessment.

In the recent clinical trials in patients with IPF, the primary endpoint of the change in FVC has been evaluated after treatment for one year [11]. However, it is not easy to conduct a clinical trial on a large scale and over a prolonged period to assess the efficacy of investigational new drugs for IPF. The recent experience of therapy for IPF with antifibrotic drugs has shown that an interval of three to six months is sufficient to evaluate the change in FVC [26]. Therefore, our study design might prove suitable for assessing the efficacy of novel antifibrotic agents, although it is unclear whether the number of patients examined is sufficient for the analyses.

The design of this study incorporated three cohorts: patients previously treated with pirfenidone (Cohort P), patients previously treated with nintedanib (Cohort N), and pirfenidone/nintedanib treatment naïve patients (Cohort U) in order to maximize efficiency by increasing the likelihood of a positive signal. %FVC change rate at Week 6 was selected as a secondary endpoint in order to explore the early response of TAS-115. FVC, VC, and DLco are considered to be predictive factors for prognosis in IPF; therefore, changes in these parameters from baseline to Weeks 6, 13, and 26 were selected as secondary endpoints.

4. Conclusion

This is the first clinical study of TAS-115 in IPF patients both untreated and treated with anti-fibroic drugs. Furthermore, to our knowledge, this is the first clinical study in IPF patients who have been treated with antifibrotic drugs (second-line treatment setting; Cohort P and Cohort N). The aims of this early stage exploratory clinical study were to evaluate the efficacy and safety of TAS-115. The therapeutic effect in IPF patients was assessed by the intra-patient difference in % FVC change rate (decline slope) at Week 13 from baseline, which is a new method for evaluating clinical efficacy in early stage clinical trials in IPF patients. The study design might prove useful for screening novel antifibrotic drugs for IPF, although the design will require further

validation in the future.

Funding

This work was funded by Taiho Pharmaceutical Co., Ltd.

CRediT authorship contribution statement

Yasuhiko Nishioka: Conceptualization, Investigation, Writing – review & editing. **Sakae Homma:** Conceptualization, Investigation, Writing – review & editing. **Takahito Okubo:** Conceptualization, Writing – review & editing, Project administration. **Arata Azuma:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YN reports grants and personal fees from Taiho Pharmaceutical Co., Ltd, during the conduct of the study; grants and personal fees from Nippon Boehringer Ingelheim Co., Ltd., grants and personal fees from Shionogi Co., Ltd., outside the submitted work; SH reports grants and personal fees from Taiho Pharmaceutical Co., Ltd, during the conduct of the study; TO reports being an employee of Taiho Pharmaceutical Co., Ltd; AA reports personal fees from Taiho Pharmaceutical Co., Ltd, during the conduct of the study; grants and personal fees from Boehringer Ingelheim, grants from Shionogi Co. Ltd, outside the submitted work.

Acknowledgements

We thank Taiho Pharmaceutical for funding to conduct this study. Medical writing assistance, supported financially by Taiho Pharmaceutical, was provided by Dr. Tetsuji Asao of SunFlare, Co., Ltd., Tokyo, Japan, during the preparation of this manuscript. 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.

References

[1] American Thoracic Society, European Respiratory Society, American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias, Am. J. Respir. Crit. Care Med. 165 (2002) 277–304, https://doi.org/10.1164/ajrccm.165.2.ats01.

[2] W.D. Travis, U. Costabel, D.M. Hansell, T.E. King Jr., D.A. Lynch, A.G. Nicholson, et al., An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias, Am. J. Respir. Crit. Care Med. 188 (2013) 733–748, https://doi.org/10.1164/rccm.201308-1483ST.

[3] R.M. du Bois, Strategies for treating idiopathic pulmonary fibrosis, Nat. Rev. Drug Discov. 9 (2010) 129–140, https://doi.org/10.1038/nrd2958.

[4] M. Natsuizaka, H. Chiba, K. Kuronuma, M. Otsuka, K. Kudo, M. Mori, et al., Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences, Am. J. Respir. Crit. Care Med. 190 (2014) 773–779, https://doi.org/10.1164/rccm.201403-0566oc.

[5] E.B. Meltzer, P.W. Noble, Idiopathic pulmonary fibrosis, Orphanet J. Rare Dis. 3 (2008) 8, https://doi.org/10.1186/1750-1172-3-8.

[6] L. Richeldi, H.R. Collard, M.G. Jones, Idiopathic pulmonary fibrosis, Lancet 389 (2017) 1941–1952, https://doi.org/10.1016/s0140-6736(17)30866-8.

[7] L. Nalysnyk, J. Cid-Ruzafa, P. Rotella, D. Esser, Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature, Eur. Respir. Rev. 21 (2012) 355–361, https://doi.org/10.1183/09059180.00002512.

[8] S. Homma, M. Bando, A. Azuma, S. Sakamoto, K. Sugino, Y. Ishii, et al., Japanese guideline for the treatment of idiopathic pulmonary fibrosis, Respir Investig 56 (2018) 268–291, https://doi.org/10.1016/j.resinv.2018.03.003.

[9] P.W. Noble, C. Albera, W.Z. Bradford, U. Costabel, M.K. Glassberg, D. Kardatzke, et al., Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials, Lancet 377 (2011) 1760–1769, https://doi.org/10.1016/s0140-6736(11)60405-4.

[10] T.E. King Jr., W.Z. Bradford, S. Castro-Bernardini, E.A. Fagan, I. Glaspole, M. K. Glassberg, et al., A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis, N. Engl. J. Med. 370 (2014) 2083–2092, https://doi.org/10.1056/nejmoa1402582.

[11] L. Richeldi, R.M. du Bois, G. Raghu, A. Azuma, K.K. Brown, U. Costabel, et al., Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis, N. Engl. J. Med. 370 (2014) 2071–2082, https://doi.org/10.1056/nejmoa1402584.

[12] F. Hilberg, G.J. Roth, M. Krssak, S. Kautschitsch, W. Sommergruber, U. Tontsch-Grunt, et al., BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy, Can. Res. 68 (2008) 4774–4782, https://doi.org/10.1158/0008-5472.can-07-6307.

[13] H. Oku, T. Shimizu, T. Kawabata, M. Nagira, I. Hikita, A. Ueyama, 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. 590 (2008) 400–408, https://doi.org/10.1016/j.ejphar.2008.06.046.

[14] K.R. Flaherty, M. Kolb, C. Vancheri, W. Tang, C.S. Conoscenti, L. Richeldi, Stability or improvement in forced vital capacity with nintedanib in patients with idiopathic pulmonary fibrosis, Eur. Respir. J. 52 (2018) 1702593, https://doi.org/10.1183/13993003.02593-2017.

[15] A. Tzouvelekis, T. Karampitsakos, P. Ntolios, V. Tzilas, E. Bouros, E. Markozannes, et al., Longitudinal "real-world" outcomes of pirfenidone in idiopathic pulmonary fibrosis in Greece, Front. Med. 4 (2017) 213, https://doi.org/10.3389/fmed.2017.00213.

[16] P.W. Noble, C. Albera, W.Z. Bradford, U. Costabel, R.M. du Bois, E.A. Fagan, et al., Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials, Eur. Respir. J. 47 (2016) 243–253, https://doi.org/10.1183/13993003.00026-2015.

[17] T. Corte, F. Bonella, B. Crestani, M.G. Demedts, L. Richeldi, C. Coeck, et al., Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis, Respir. Res. 16 (2015) 116, https://doi.org/10.1186/s12931-015-0276-5.

[18] G. Raghu, M. Remy-Jardin, J.L. Myers, L. Richeldi, C.J. Ryerson, D.J. Lederer, et al., Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical Practice guideline, Am. J. Respir. Crit. Care Med. 198 (2018) e44–e68, https://doi.org/10.1164/rccm.201807-1255st.

[19] K. Koyama, H. Goto, S. Morizumi, K. Kagawa, H. Nishimura, S. Sato, et al., The tyrosine kinase inhibitor TAS-115 attenuates bleomycin-induced lung fibrosis in mice, Am. J. Respir. Cell Mol. Biol. 60 (2019) 478–487, https://doi.org/10.1165/rcmb.2018-0098oc.

[20] F. Grimminger, A. Günther, C. Vancheri, The role of tyrosine kinases in the pathogenesis of idiopathic pulmonary fibrosis, Eur. Respir. J. 45 (2015) 1426–1433, https://doi.org/10.1183/09031936.00149614.

[21] T. Doi, N. Matsubara, A. Kawai, N. Naka, S. Takahashi, H. Uemura, et al., Phase I study of TAS-115, a novel oral multi-kinase inhibitor, in patients with advanced solid tumors, Invest. N. Drugs 38 (2020) 1175–1185, https://doi.org/10.1007/s10637-019-00859-4.

[22] M. Kubota, H. Kobayashi, P. Quanjer, H. Omori, K. Tatsumi, M. Kanazawa, Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values, Respir Investig 52 (2014) 242–250, https://doi.org/10.1016/j.resinv.2014.03.003.

[23] P.I. Latsi, R.M. du Bois, A.G. Nicholson, T.V. Colby, D. Bisirtzoglou, A. Nikolakopoulou, et al., Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends, Am. J. Respir. Crit. Care Med. 168 (2003) 531–537, https://doi.org/10.1164/rccm.200210-1245oc.

[24] H.R. Collard, T.E. King Jr., B.B. Bartelson, J.S. Vourlekis, M.I. Schwarz, K.K. Brown, Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 168 (2003) 538–542, https://doi.org/10.1164/rccm.200211-1311oc.

[25] K.R. Flaherty, J.A. Mumford, S. Murray, E.A. Kazerooni, B.H. Gross, T.V. Colby, et al., Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia, Am. J. Respir. Crit. Care Med. 168 (2003) 543–548, https://doi.org/10.1164/rccm.200209-1112oc.

[26] E.F. Fabrellas, R.P. Sánchez, C.S. Abad, G.J. Samper, Prognosis and follow-up of idiopathic pulmonary fibrosis, Med. Sci. 6 (2018) 51, https://doi.org/10.3390/medsci6020051.