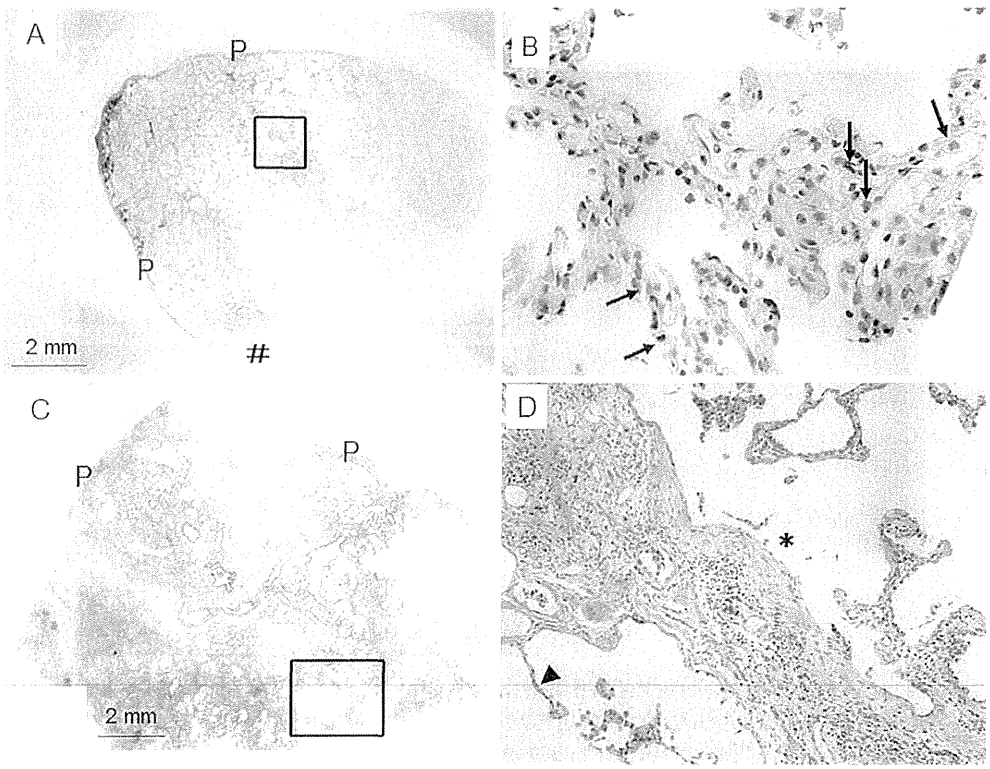

Figure 3. Histopathological findings of the surgical biopsy specimens of the left lung in April 2009. (A) The lung tissue from the upper lobe (lt. S^{1+2}) showed mildly patchy fibrotic lesions consistent with usual interstitial pneumonia (#) [Hematoxylin and Eosin (H&E) staining, 1×]. P, visceral pleura. Bar=2mm. (B) A high magnification of the square frame in (A) showed cuboidal epithelial cells with foamy cytoplasm lining the alveolar walls (arrows) (H&E staining, 40×). (C) The lung tissue from the lower lobe (lt. S^{10}) showed extensive, periacinar dominant fibrotic lesions (H&E staining, 1×). P: visceral pleura. Bar=2mm. (D) A high magnification image of the square frame in (C) showed fibrotic lesions with loss of normal alveolar structure and a fibroblast focus (*). Adjacent alveolar walls were almost normal (arrowhead) (H&E staining, 10×).

months after examination, while all patients with an HRCT score under 2 with non-diffuse interstitial shadows survived within one year after examination (11). Our patient was over 50 years, and his HRCT findings already showed diffuse reticular opacities and traction bronchiectasis in the bilateral lung fields, consistent with a Brantly's score of 3 on the initial HRCT. From these clinical findings, we may have recognized rapid progression and poor prognosis in this patient at the time of diagnosis.

The postmortem examination showed DAD and ring-like cystic lesions formed in the process of DAD. These pathological findings were not observed in the tissues from the VATS lung biopsy. After the diagnosis, rapid deterioration of the patient's clinical symptoms and HRCT findings, including reticular opacities and traction bronchiectasis, occurred; however, we believe the progression was not an acute exacerbation of interstitial pneumonia for two reasons. In this case, new ground-glass opacity or consolidation did not occur abruptly, and we did not observe a rapid increase in the patient's serum levels of KL-6, SP-D and SP-A [previously reported in the acute exacerbation of IPF (12)] (data not shown). Alveolar epithelial apoptosis is hypothesized to be intimately related to pulmonary fibrosis in IPF (13) and HPS (2, 3). Bleomycin-induced apoptosis of alveolar epithelial type II cells is promoted in the murine model of HPS (compared to wild-type mice) (14). We speculate that some weak stimuli may have led to the occurrence of rapid deterioration with DAD pattern in our patient, although this presentation was not typical of an acute exacerbation. Although supplementation of high concentrations of oxygen may cause pulmonary injury, we speculate that the progression of pulmonary fibrosis is due to a gradual deterioration with DAD pattern. These pathological changes between the specimens from VATS and autopsy may explain the mechanism of progression in HPS patients.

Current treatment strategies, such as corticosteroids or other immunosuppressive agents, generally fail to curtail this pulmonary disease progression in Japanese HPS patients (15-17). Pirfenidone is approved for the treatment of IPF, inhibits both inflammatory and fibrotic cytokines, and has antioxidant effects (18-21). The inhibitory effects of pirfenidone on alveolar macrophage cytokine secretion have

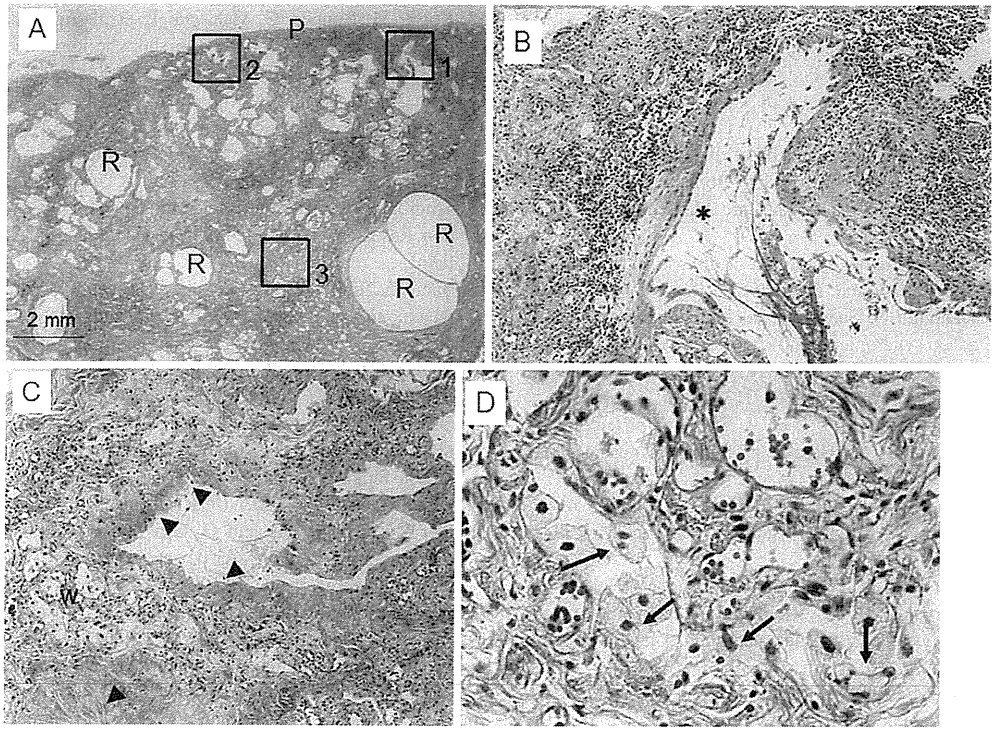

Figure 4. **Autopsy findings of the patient in September 2009. (A) The upper lobe tissue of the left lung (lt. S^{1+2}) showed extensive fibrosis with numerous ring-like lesions (R) [Hematoxylin and Eosin (H&E) staining, 1×]. P, visceral pleura. Bar=2mm. (B) A high magnification image of the square frame 1 in (A) showed a fibroblast focus covered with flattened epithelial cells (*) and a fibrotic lesion with moderate infiltration of lymphoid cells and mucin stasis in the dilated air space at the level of a respiratory bronchiole (H&E staining, 10×). (C) A high magnification image of the square frame 2 in (A) showed hyalinous materials without epithelial lining (arrowheads) that covered the wall of the alveolar ducts. In between, there were a few alveolar walls with mild, fibrous thickening (W) (H&E staining, 10×). (D) A high magnification image of the square frame 3 in (A) showed some cuboidal epithelial cells with foamy cytoplasm (arrows) (H&E staining, 40×).**

also been reported in patients with HPS1 (22). In a previous double-blind, randomized, placebo-controlled trial of 21 adult HPS patients, pirfenidone was shown to slow the progression of pulmonary fibrosis associated with HPS, especially in patients with an initial forced vital capacity (FVC) >50% of the predicted (6). This result is similar to the study conducted by Azuma et al. who showed that pirfenidone exerted more pronounced effects in IPF patients with mild impairments (23). Our patient may have shown poor response to pirfenidone because his FVC at pirfenidone initiation was 36.6% of the predicted value. Recently, O'Brien et al. reported that pirfenidone showed no inhibitory effects on the decline of FVC in HPS patients with an FVC >50% (7). A limited number of patients were enrolled in this trial, and large-scale trials are necessary to conclude that pirfenidone is not effective. Pirfenidone may not be an epoch-making drug, and the development of other drugs is suggested for HPS patients.

We herein detected DAD pattern lesions and ring-like cystic lesions in the autopsy specimens; these lesions were not observed in the specimens from VATS. We suspect that a rapid deterioration with DAD pattern may be one of the progression patterns observed in HPS patients. Further investigation of the HPS pathogenesis is necessary for improving the prognosis in HPS patients, which may be a therapeutic avenue to this intractable disease.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer

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Key words

Erlotinib, interstitial lung disease, Japanese, non-small-cell lung cancer, surveillance

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Interstitial lung disease (ILD) occurrence and risk factors were investigated in the Japanese non-small-cell lung cancer, post-marketing, large-scale surveillance study, POLARSTAR. All patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009 were enrolled. Primary endpoints were patterns of ILD and risk factors for onset of ILD and ILD-related death. Overall survival, progression-free survival, and occurrence of adverse drug reactions were secondary endpoints. Interstitial lung disease was confirmed in 429 (4.3%) patients. Concurrent/previous ILD (hazard ratio, 3.19), emphysema or chronic obstructive pulmonary disease (hazard ratio, 1.86), lung infection (hazard ratio, 1.55), smoking history (hazard ratio, 2.23), and period from initial cancer diagnosis to the start of treatment (<360 days; hazard ratio, 0.58) were identified as significant risk factors for developing ILD by Cox multivariate analysis. Logistic regression analysis identified Eastern Cooperative Oncology Group performance status 2–4 (odds ratio, 2.45 [95% confidence interval, 1.41–4.27]; $P = 0.0016$), ≤50% remaining normal lung area (odds ratio, 3.12 [1.48–6.58]; $P = 0.0029$), and concomitant honeycombing with interstitial pneumonia (odds ratio, 6.67 [1.35–32.94]; $P = 0.02$) as poor prognostic factors for ILD death. Median overall survival was 277 days; median progression-free survival was 67 days. These data confirm the well-characterized safety profile of erlotinib. Interstitial lung disease is still an adverse drug reaction of interest in this population, and these results, including ILD risk factors, give helpful information for treatment selection and monitoring. Erlotinib efficacy was additionally confirmed in this population. (POLARSTAR trial ML21590.)

Erlotinib is an orally administered EGFR TKI that has demonstrated survival benefits over placebo (median OS 6.7 *vs* 4.7 months, respectively; $P = 0.002$) with acceptable tolerability in previously treated patients with NSCLC.[1] Promising survival data were also reported in two Japanese phase 2 trials of erlotinib in patients with advanced NSCLC (median OS 13.5–14.7 months).[2,3] This led to the approval of erlotinib in Japan for the treatment of patients with recurrent/advanced NSCLC after failure on at least one prior chemotherapy regimen.

Interstitial lung disease has been reported as an AE of special interest in erlotinib-treated Japanese patients with NSCLC in 4.9% (6/123) of patients with a mortality rate of 2.4% (3/123 patients).[2–4] Similar incidences of ILD have been reported in Japanese patients with NSCLC treated with the EGFR TKI gefitinib, suggesting this may be a class-related AE.[5,6]

Risk factors for developing ILD have been previously reported primarily in gefitinib-treated patients. Kudoh *et al.*[6] reported old age, smoking history, pre-existing ILD, poor ECOG PS, short duration since NSCLC diagnosis, and ≤50% normal lung area as ILD risk factors, with all of the factors, except ECOG PS and short duration since NSCLC diagnosis, also being associated with poor ILD prognosis (fatal ILD).

Hotta *et al.*[7] reported existing pulmonary fibrosis, poor ECOG PS, and prior irradiation as risk factors for ILD. Pre-existing pulmonary fibrosis and poor ECOG PS have also been shown to be associated risk factors for ILD in patients treated with either gefitinib or erlotinib.[8]

POLARSTAR was a large-scale surveillance study including all Japanese patients with NSCLC treated with erlotinib,[9] undertaken as a post-approval commitment in Japan to monitor safety and efficacy. The objectives were to obtain decisive information on the incidence of ILD, risk factors for developing ILD, and the efficacy of erlotinib. Here, we report the final analysis of the POLARSTAR surveillance study investigating the safety and efficacy of erlotinib treatment in Japanese patients with NSCLC.

Methods

Study design. All patients with unresectable, recurrent /advanced NSCLC who were treated with erlotinib in Japan between December 2007 and October 2009 were enrolled. Eligible patients receiving erlotinib (150 mg orally, once daily), from the 1027 institutions that could prescribe erlotinib, were monitored until erlotinib therapy termination or completion of 12 months of treatment. The study was approved by the relevant ethics committees and patients gave informed consent to participate in the analysis.

Assessments. Demographic and baseline data were collected for each patient, including age, gender, body mass index, tumor histology, ECOG PS, smoking history, and medical history (including hepatic dysfunction, renal dysfunction, cardiovascular disease, and lung disorders). Safety data were collected at 1, 6, and 12 months after the start of erlotinib therapy. All AE reports were collected and graded using the National Cancer Institute Common Terminology Criteria for AEs version 3.0 and coded using the Medical Dictionary for Regulatory Activities version 14.1 thesaurus terms.

Outcome measures. Primary endpoints were patterns of occurrence of ILD and risk factors for onset of ILD. Overall survival and PFS were secondary endpoints and were assessed according to the treating physician's standard clinical practice. The pattern of ADRs, excluding ILD, was an additional secondary endpoint.

Statistical analyses. The sample size determination is previously described.[9] Briefly, 3000 patients were to be enrolled to detect an AE in one case out of 3000 patients with at least a power of 95%; however, during enrolment, target accrual was increased to 10 000 patients by the Japanese Health Authority to further evaluate the safety and efficacy of erlotinib. The increased patient number allows high sensitivity regarding low-frequency ADRs. The safety population comprised all patients who received erlotinib and had case report form data available. The efficacy population comprised all patients included in the safety population, except those where erlotinib therapy was prescribed off-label (i.e. in the first-line setting) at the time of this study, or where a patient's therapeutic history was unknown.

Median PFS and OS were estimated using Kaplan–Meier methodology. Patients without data for the duration of the observation period or from the time of treatment initiation were excluded from the PFS analyses.

Statistical analyses were carried out using Statistical Analysis Software version 9.1 and 9.2 (SAS Institute, Cary, NC). Multivariate Cox regression analysis using a stepwise model was carried out to determine risk factors for ILD; occurrence of ILD was used as the dependent variable. Exploratory variables with $P > 0.05$ were not included in the final model. In the final step, additional multivariate analyses were carried out to investigate two-factor interactions; statistical significance was set at $P < 0.05$. This method is described in more detail in the interim analysis publication.[9]

To examine factors affecting poor prognosis in ILD, a stepwise, 5% significance level, multivariate logistic regression analysis was carried out with an analysis set of 310 patients in whom an ILD diagnosis was confirmed by the ILD Review Committee. The target variable was fatal ILD; exploratory variables included gender, age, primary lesion, histological type, smoking history, ECOG PS, honeycomb lung, non-metastatic lesions, and remaining normal lung. The exploratory variables were chosen by the results of a univariate analysis using ILD death as the target variable, with baseline characteristics and characteristics previously reported to affect poor ILD prognosis as the univariate exploratory variables.

Results

A total of 10 708 patients were enrolled in this study. Of these, 9909 patients were evaluated for the final safety analysis and 9663 patients were evaluated for the final efficacy analysis (Fig. 1). Baseline characteristics are shown in Table 1. Of note, more males than females were enrolled; the majority of patients had adenocarcinoma histology (80.9%) and most had ECOG PS 0–1 (74.0%).

Safety analysis. Adverse drug reactions were reported in 79.1% (7835/9909) of patients, the most common being skin disorders (67.4%), including rash (60.9%), diarrhea (21.5%), hepatitis, hepatic failure and hepatic function disorder (9.8%), eye disorders (3.3%) and hemorrhage (1.6%; Table 2). Median time to onset of ADRs was 9 days for rash, 8 days for diarrhea, 13 days for hepatitis, hepatic failure, and hepatic function

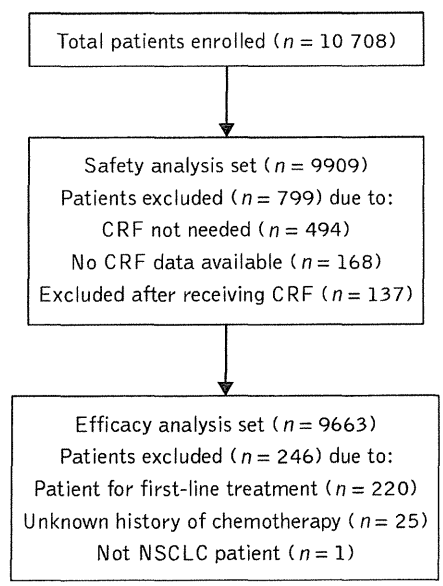

Fig. 1. Disposition of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009 and who were included in the final analysis. CRF, case report form; NSCLC, non-small-cell lung cancer.

Table 1. Baseline characteristics of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009

Characteristic	Patients, *n* (%) (*n* = 9909)
Gender	
Male	5300 (53.5)
Female	4609 (46.5)
Age	
<65 years	4466 (45.1)
65–74 years	3382 (34.1)
≥75 years	2059 (20.8)
Histology	
Adenocarcinoma	7950 (80.9)
Squamous cell	1285 (13.1)
Large cell	155 (1.6)
Other	438 (4.5)
ECOG PS	
0–1	7315 (74.0)
2–4	2576 (26.0)
Smoking history	
No	4366 (44.9)
Yes	5367 (55.1)
Number of previous treatment lines	
0	220 (2.2)
1	2481 (25.1)
2	2646 (26.8)
3	1993 (20.2)
4	1546 (15.6)
≥5	998 (10.1)
Previous gefitinib treatment	
Yes	4396 (44.7)
No	5446 (55.3)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Incidence of the most common adverse drug reactions (ADRs) in patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009

ADR	All grades		Grade ≥3	
	Patients		Patients	
	n	%	*n*	%
ILD	429	4.3	257	2.6
Skin disorder				
Rash	6032	60.9	673	6.8
Dry skin	738	7.4	30	0.3
Pruritus	351	3.5	13	0.1
Paronychia	654	6.6	77	0.8
Hepatitis, hepatic failure, hepatic function disorder	976	9.8	183	1.8
Diarrhea	2133	21.5	137	1.4
Eye disorders	331	3.3	19	0.2
Corneal disorders	186	1.9	11	0.1
Hemorrhage	158	1.6	46	0.5
Gastrointestinal hemorrhage	39	0.4	20	0.2

ILD, interstitial lung disease.

disorder, 15 days for eye disorders, and 16 days for hemorrhage.

Interstitial lung disease. *Incidence.* Of the patients analyzed, 491 patients had 497 ILD-like events, of which 62 events were deemed non-ILD by the independent ILD Review Committee. In total, 429 (4.3%) patients were classified as having ILD (310 confirmed and reported by the ILD Review Committee, 119 patients not confirmed by the ILD Review Committee due to not having an evaluated image [*n* = 93], too difficult to distinguish from tumor progression [*n* = 4], and too difficult to distinguish from pneumonia due to insufficient evaluable images or clinical findings [*n* = 22] were still classified as ILD), with an overall mortality rate of 1.5% and a mortality rate of 35.7% in patients with ILD.

The majority of ILD cases (58.5%) were reported within 4 weeks of receiving erlotinib. The incidence of ILD (per 100 patient-weeks) was 0.63–0.81 within 4 weeks of the start of erlotinib treatment and 0.09–0.27 from 6 weeks after the start of erlotinib treatment (Fig. 2). Univariate analysis identified patients who were female, patients with non-adenocarcinoma histology, those with a period of treatment from initial NSCLC diagnosis to the start of treatment <360 days, concomitant or previous emphysema or COPD, concomitant or previous ILD, concomitant or previous lung infections, concomitant hepatic disorders, concomitant renal disorders, history of allergies, smoking history, ECOG PS 2–4, prior chest radiotherapy, pretreatment lactate dehydrogenase, and no previous treatment with gefitinib as risk factors for ILD development (Table 3). Age at start of treatment, body mass index, concurrent cardiovascular disorders, number of chemotherapy regimens and previous treatment with gemcitabine were variables that were not identified as risk factors from the univariate analysis. Multivariate analysis showed that concurrent/previous ILD (HR, 3.19), concurrent/previous emphysema or COPD (HR, 1.86), concurrent/previous lung infection (HR, 1.55), smoking history (HR, 2.25), and period from initial NSCLC diagnosis to the start of treatment (<360 days; HR, 0.58) were identified as significant risk factors for developing ILD by multivariate analysis (Table 3).

Outcomes of ILD. Of the confirmed cases of ILD, 75 (17.5%) patients fully recovered, 154 (35.9%) patients improved their condition, 32 (7.5%) patients did not recover, five (1.2%) patients had sequelae, 153 (35.7%) patients died, and 10 (2.3%) patients had unknown outcomes.

The outcome of ILD by CT image pattern was investigated in 283 patients out of the 310 patients deemed as having confirmed ILD by the independent ILD Review Committee. Diffuse alveolar damage-like pattern on CT was defined as abnormalities that showed non-segmental ground-glass attenuation or airspace consolidation with traction bronchiectasis and loss of volume. In the 63 patients with CT-DAD-like pattern, six (9.5%) patients recovered, 12 (19.1%) patients improved, three (4.8%) patients did not recover, one (1.6%) patient had residual ILD sequelae, and 41 (65.1%) patients died. In the 220 patients with a CT-non-DAD-like pattern, 37 (16.8%) patients recovered, 95 (43.2%) patients improved, 13 (5.9%) patients did not recover, one (0.5%) patient had residual ILD sequelae, 71 (32.3%) patients died, and three (1.4%) patients had unknown outcomes.

Fatal outcome of ILD. The multivariate logistic analysis identified ECOG PS 2–4 (OR, 2.45), ≤50% remaining normal lung area (OR, 3.12), and concomitant honeycombing with

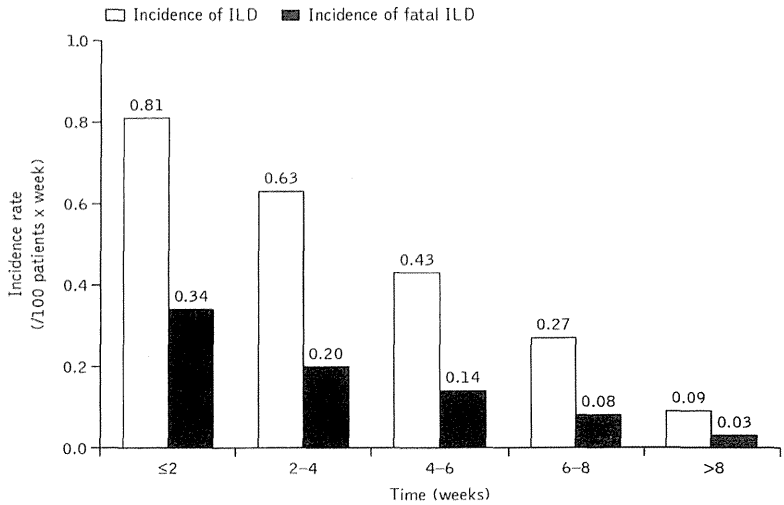

Fig. 2. Incidence rate of interstitial lung disease (ILD) stratified by time from start of erlotinib treatment to onset of ILD. The 34 patients without data for either the duration of observation or the time from the start of erlotinib treatment to the onset of ILD were excluded from the analysis. Value determined by dividing the number of patients developing ILD during the specified duration of observation by the patient-days during the observation period (total duration [number of days] of observation of all patients receiving erlotinib during the specified duration of observation).

Table 3. Cox regression univariate and multivariate analysis of factors affecting the incidence of interstitial lung disease (ILD) in patients with unresectable, recurrent/advanced non-small-cell lung cancer (NSCLC) who were treated with erlotinib in Japan between December 2007 and October 2009

Variables	Criterion variable	Evaluation variable	X^2 value	*P*-value	HR	95% CI
Univariate analysis						
Gender	Male	Female	76.3424	<0.0001	0.390	0.315–0.481
Age (years)	<55	≥55	2.257	0.133	1.256	0.933–1.692
Body mass index (kg/m^2)	<25	≥25	2.4468	0.1178	0.788	0.585–1.062
Histology	Adenocarcinoma	Non-adenocarcinoma	32.0958	<0.0001	1.847	1.494–2.283
Period from initial NSCLC diagnosis to the start of treatment	<360 days	≥360 days	20.1885	<0.0001	0.638	0.525–0.776
Concurrent/previous emphysema or COPD	No	Yes	85.1118	<0.0001	3.071	2.420–3.898
Concurrent/previous ILD	No	Yes	88.7072	<0.0001	3.862	2.915–5.116
Concurrent/previous lung infection	No	Yes	18.7152	<0.0001	1.979	1.453–2.697
Concurrent hepatic disorder	No	Yes	4.9716	0.0258	1.426	1.044–1.949
Concurrent renal disorder	No	Yes	9.1417	0.0025	1.611	1.183–2.195
Concurrent cardiovascular disorder	No	Yes	2.8576	0.0909	1.191	0.973–1.459
History of allergies	No	Yes	5.2846	0.0215	1.358	1.046–1.764
Smoking history	No	Yes	87.4412	<0.0001	2.896	2.318–3.620
ECOG PS	0–1	2–4	20.0203	<0.0001	1.620	1.311–2.001
Prior chest radiation therapy	No	Yes	11.9016	0.0006	1.431	1.167–1.753
Baseline lactate dehydrogenase†	–	–†	7.0077	0.0081	1	1–1
Number of chemotheraphy regimens for the primary diseases	–	–†	1.2809	0.2577	1.033	0.977–1.092
History of gemcitabine treatment	No	Yes	0.1141	0.7355	0.967	0.797–1.174
History of gefitinib treatment	No	Yes	38.7111	<0.0001	0.517	0.420–0.636
Multivariate analysis						
Concurrent/previous ILD	No	Yes	55.3796	<0.0001	3.187	2.349–4.325
Smoking history	No	Yes	34.1327	<0.0001	2.246	1.712–2.946
Concurrent/previous emphysema or COPD	No	Yes	20.704	<0.0001	1.860	1.424–2.431
Period from initial NSCLC diagnosis to the start of treatment	<360 days	≥360 days	19.3818	<0.0001	0.581	0.456–0.740
Concurrent/previous lung infection	No	Yes	6.5905	0.0103	1.550	1.109–2.165
ECOG PS	0–1	2–4	8.9467	0.0028	1.431	1.131–1.809
History of gefitinib treatment	No	Yes	5.3133	0.0212	0.729	0.557–0.954
Number of chemotherapy regimens†	–	–†	10.4136	0.0013	1.121	1.046–1.201

Objective variable: occurrence or non-occurrence of ILD. Explanatory variables: gender, age, body mass index, histological type, concurrent/previous emphysema or chronic obstructive pulmonary disease (COPD), concurrent/previous ILD, concurrent/previous lung infection, concomitant hepatic disorder, concomitant renal disorder, period from initial NSCLC diagnosis to the start of treatment, concomitant cardiovascular disease, history of allergies, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), radiotherapy (chest), pretreatment lactate dehydrogenase, number of chemotherapy regimens for the primary disease, history of gemcitabine treatment, history of gefitinib treatment. †Analyzed as a continuous quantity. NSCLC, non-small-cell lung cancer; ILD, interstitial lung disease.; CI, confidence interval; HR, hazard ratio.

Table 4. Interstitial lung disease (ILD) poor prognosis risk factors from the final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Risk factors for ILD-related death	Criterion variable	Evaluation variable	X^2 value	*P*-value	OR	95% CI
ECOG PS 2–4	0–1	2–4	9.974	0.0016	2.45	1.41–4.27
≤50% normal lung area	>50	≤50	8.896	0.0029	3.12	1.48–6.58
Concomitant honeycombing	No	Yes	5.414	0.02	6.67	1.35–32.94

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio.

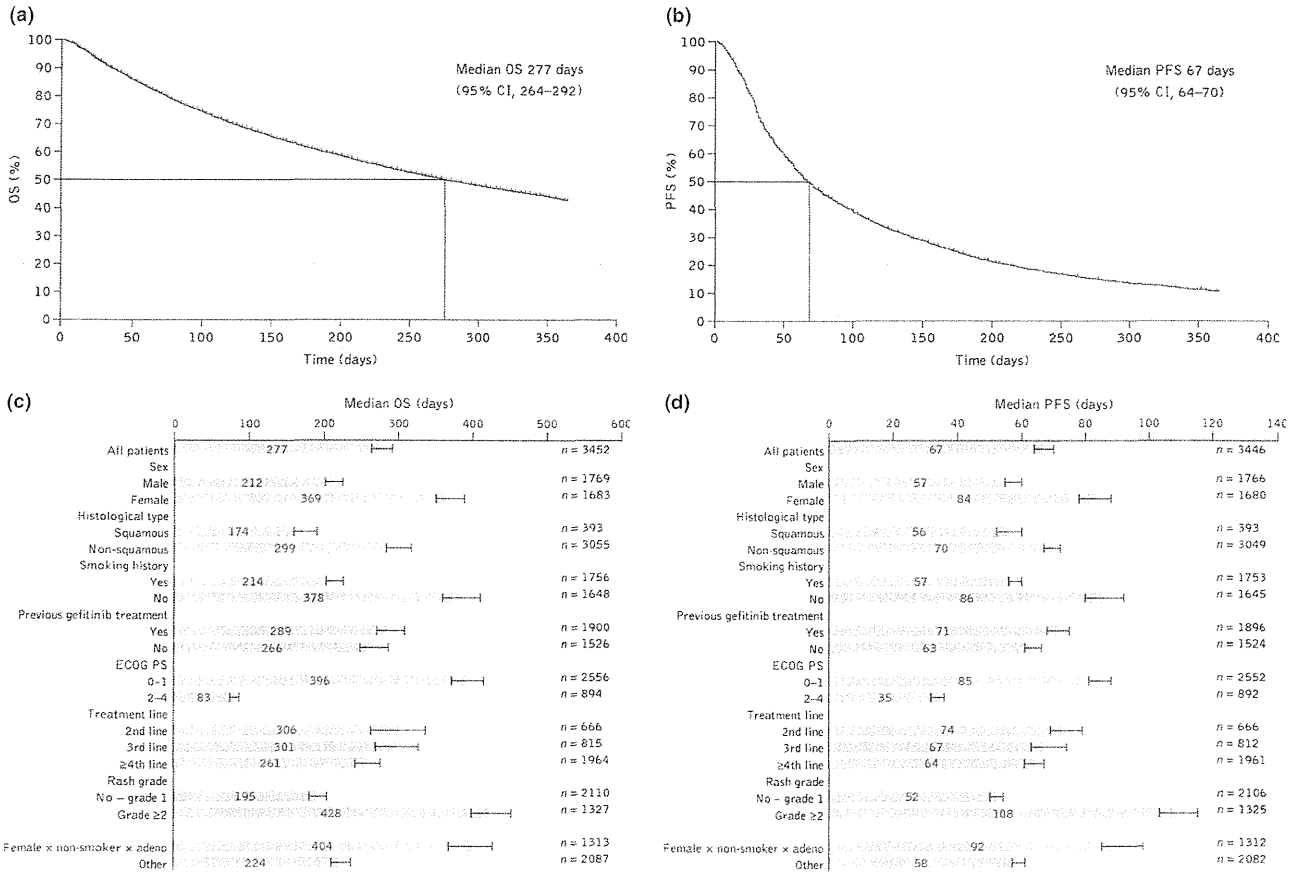

Fig. 3. (a) Overall survival (OS) and (b) progression-free survival (PFS) assessed by Kaplan–Meier methodology in the overall population of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009; (c) median OS and (d) PFS in patient subpopulations. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

interstitial pneumonia (OR, 6.67) as poor prognostic factors for ILD death (Table 4).

A total of 12 patients reported concomitant honeycombing and interstitial pneumonia; of these patients, nine patients died of ILD, two patients improved their condition, and one patient did not recover. Of those who died, eight were determined as having CT-non-DAD-like pattern on CT scan and the remaining patient was determined as having CT-DAD-like pattern.

Efficacy. Median OS was 277 days (95% CI, 264–292), with a 6-month survival rate of 62.6% and a 12-month survival rate of 42.8% (Fig. 3a). Median PFS was 67 days (95% CI, 64–70), with a 6-month progression-free rate of 25.8% and a 12-month progression-free rate of 10.6% (Fig. 3b). Compared with the overall population, median OS and PFS appeared to be longer in female patients, non-smokers, patients with ECOG PS 0–1, and patients with grade ≥2 rash (Fig. 3c,d).

Discussion

The development of drug-induced acute pulmonary disorders or interstitial pneumonia caused by EGFR TKIs is a common problem; this has particular importance in Japan, because a variety of evidence has suggested that Japanese populations are more vulnerable to these disorders. This large-scale POLARSTAR study provides further decisive information on this issue. Final data from the POLARSTAR study confirm that erlotinib has a well-characterized safety profile with proven efficacy in Japanese patients in routine clinical practice.

In the final analysis from POLARSTAR, the rates of ILD development and mortality in patients with ILD (4.3% and 35.7%, respectively) were comparable with the ILD-associated incidence rates of 3–5% and mortality rates of 27.9–50.0% previously reported among Japanese patients with NSCLC and ILD treated with gefitinib or erlotinib.[2,3,5,6,9] In the POLARSTAR analysis, it was shown that ILD onset was typically soon after initiation of erlotinib, with the highest incidence occurring during the first 4 weeks. Physicians should therefore monitor patients for the symptoms of ILD, which usually occur within 8 weeks of treatment initiation. These findings are further supported by those reported in Japanese NSCLC studies with gefitinib.[5,6]

The risk factors identified as significant primary risk factors (HR, ≥1.5) for ILD occurrence or exacerbation using a Cox proportional hazards multivariate analysis were concurrent/previous ILD, concurrent/previous lung infection, concurrent/previous emphysema or COPD, and smoking history. Cox proportional hazards multivariate analysis was selected for this assessment as the authors considered that a time-dependent analysis was needed, as there was no information regarding the ILD development point in the initial analysis. Concurrent /previous emphysema or COPD was newly identified as a significant primary risk factor for ILD occurrence when analyzed in 9909 patients compared with the result of the interim analysis of 3488 patients (Table 5).[9,10] As ILD is a collective term for a variety of different lung conditions, it is important to be careful not to misdiagnose conditions as ILD, as this will affect the risk factor analysis.

The period from initial NSCLC diagnosis to the start of treatment (<360 days) was not considered as a risk factor for ILD that needed to be highlighted at this time (HR, 0.58), as the clinical grounds for this factor were not clear. Stage of progression of primary disease or bias of observational period from initial NSCLC diagnosis to termination of treatment were speculated to be the reason; however, details of these reasons are uncertain. In contrast to this analysis, risk factors for ILD associated with gefitinib have been reported as ECOG PS ≥2, smoking history, concomitant interstitial pneumonia, and prior chemotherapy.[5,7,8]

The multivariate analysis identified ECOG PS 2–4, ≤50% remaining normal lung area and concomitant honeycombing with interstitial pneumonia as poor prognostic factors for ILD death in POLARSTAR. Many patients with idiopathic interstitial pneumonias have idiopathic pulmonary fibrosis or non-specific interstitial pneumonia, which have a heterogeneous natural progression, with some patients remaining stable for extended periods, while others show steady worsening of the condition.[11] Some patients with chronic idiopathic interstitial pneumonias, such as idiopathic pulmonary fibrosis and non-specific interstitial pneumonia, experience acute exacerbations characterized by suddenly progressive and severe respiratory failure, with new lung opacities and pathological lesions of DAD.[12] It should be noted that there are racial differences between Mongolians (including the Japanese) and Caucasians in the frequency of acute exacerbations.[13] In the POLARSTAR study, the outcome of ILD by CT image pattern was investigated in 283 patients out of the 310 patients deemed as having confirmed ILD by the independent ILD Review Committee. The mortality rate for ILD among patients who were deemed to have CT-DAD-like pattern was higher than that seen among patients who were deemed as having CT-non-DAD-like pattern (65.1% *vs* 32.2%, respectively). Those patients with honeycombing and interstitial pneumonia (n = 12) had a high risk of poor prognosis, regardless of their CT pattern. Therefore, physicians should be actively aware of the symptoms of ILD and it is suggested to carefully monitor for these symptoms by CT image or X-ray throughout the disease course. Once physicians recognize ILD, they should immediately discontinue the EGFR TKI and should take the necessary steps to manage the ILD.

The final efficacy results from POLARSTAR are in line with the results of our interim analysis of the study (Table 6).[9] The final efficacy results (median OS, 277 days; median PFS, 67 days) were also comparable with efficacy reported in previous clinical trials of erlotinib treatment. The BR.21 study reported median PFS of 2.2 months (67 days) versus 1.8 months (55 days) and OS of 6.7 months (203 days) versus 4.7 months (143 days) for erlotinib and placebo, respectively, in the second- or third-line setting.[1] Kubota *et al.* investigated second-line erlotinib in Japanese patients, resulting in a median PFS of 77 days and OS of 14.7 months (447 days).[2] In a sec-

Table 5. Comparison of the interstitial lung disease (ILD) analysis from the interim and final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Endpoint	Interim analysis (safety, n = 3488) (efficacy, n = 3453)	Final analysis (safety, n = 9909) (efficacy, n = 9663)
ILD analysis		
Patients with confirmed ILD, n (%)	158 (4.5)	429 (4.3)
ILD-related mortality rate, %	1.6	1.5
ILD-related mortality rate in ILD patients	34.8	35.7
Risk factors for ILD development, HR		
Previous/concurrent ILD	4.1	3.2
Previous/concurrent Emphysema or COPD	–	1.9
Previous/concurrent lung infection	2.0	1.6
Smoking history	3.0	2.2
ECOG PS 2–4	1.6	1.4
<360 days from diagnosis to treatment	–	0.58

COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

Table 6. Comparison of the efficacy endpoints from the interim and final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Endpoint	Interim analysis (safety, n = 3488) (efficacy, n = 3453)	Final analysis (safety, n = 9909) (efficacy, n = 9663)
Efficacy endpoints		
Median OS, days	260	277
6-month OS rate, %	62.2	62.6
12-month OS rate, %	40.9	42.8
Median PFS, days	64	67
6-month PFS rate, %	23.7	25.8
12-month PFS rate, %	9.6	10.6

OS, overall survival; PFS, progression-free survival.

ond phase 2 study in Japanese patients with NSCLC, second-line erlotinib treatment resulted in median OS of 13.5 months (410 days).[3]

We acknowledge that there are several limitations of this study, including the fact that this was a single-arm observational study with no control group, and the lack of a strict observation period, unlike a clinical trial. The lack of information on *EGFR* mutation status is also considered a limitation as this is known to strongly affect the efficacy of erlotinib. The lack of patient selection criteria may also be seen as a limitation; however, this may mean that our study population was more representative of the actual Japanese population than would be the case in a clinical trial, especially because of the large patient population in this study. The information on EGFR TKI-associated ILD in this study is thought to be decisive; it provides valuable information for treatment considerations and monitoring in Japanese patients with *EGFR* mutant or wild-type lung cancer.

Healthcare providers should carefully observe patients during treatment with erlotinib to ascertain whether the patient has any of the risk factors detailed in this analysis. After suspicion of the onset of ILD and diagnosis by CT, it is important to follow the patient's status continuously and carefully monitor their risk level. The final safety and efficacy data from the large-scale POLARSTAR surveillance study confirm that erlotinib has a well-characterized safety profile with proven efficacy in Japanese patients; however, the risk of ILD should still be monitored.

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Disclosure Statement

KN, SK, YO, TJ, MA, NY, and MF have all participated as independent advisory board members for erlotinib, reimbursed by Chugai Pharmaceutical Co. Ltd. YO also has an immediate family member who is an employee of Chugai Pharmaceutical Co. Ltd. HA, YI, ME, TJ, MK, KK, FS, HT, AG, and YF have all participated as independent ILD Review Committee members for erlotinib, reimbursed by Chugai Pharmaceutical Co. Ltd. AS and TI are full-time employees of Chugai Pharmaceutical Co. Ltd. This trial was designed, funded, and monitored by Chugai Pharmaceutical Co. Ltd. Data were gathered, analyzed, and interpreted by Chugai with input from all authors. The corresponding author had full access to the relevant data and took full responsibility for the final decision to submit the report for publication. Although technically classed as a clinical trial, the POLARSTAR study was a non-interventional surveillance study analyzing all NSCLC patients receiving erlotinib in Japan, therefore it was not registered as a phase II/III clinical trial would be.

Abbreviations

ADR	adverse drug reaction
AE	adverse event
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	computed tomography
DAD	diffuse alveolar damage
ECOG	PS Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
HR	hazard ratio
ILD	interstitial lung disease
NSCLC	non-small-cell lung cancer
OR	odds ratio
OS	overall survival
PFS	progression-free survival
POLARSTAR	Post-Launch All-patient-Registration Surveillance in Tarceva®-treated NSCLC patients
TKI	tyrosine-kinase inhibitor

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ORIGINAL ARTICLE
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Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis

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ABSTRACT A randomised, double-blind, phase II, dose escalation trial was conducted to assess the safety, tolerability and pharmacokinetics of the tyrosine kinase inhibitor nintedanib, alone and when added to ongoing pirfenidone therapy, in Japanese patients with idiopathic pulmonary fibrosis.

50 Japanese patients were randomised to receive nintedanib or placebo in one of three cohorts (nintedanib 50 mg twice daily or 100 mg twice daily for 14 days, or 150 mg twice daily for 28 days). Patients receiving pirfenidone at inclusion were stratified to every nintedanib dose group and placebo.

Adverse events were reported in nine out of 17 patients receiving nintedanib alone and 10 out of 21 patients receiving nintedanib added to pirfenidone. All adverse events were mild or moderate in intensity. Gastrointestinal disorders were the most common adverse event. Maximum plasma concentration and area under the curve at steady state for nintedanib and its metabolites tended to be lower when nintedanib was added to pirfenidone. Nintedanib had no effect on the pharmacokinetics of pirfenidone.

In conclusion, further study is needed to evaluate the safety and tolerability profile of nintedanib when added to pirfenidone in patients with idiopathic pulmonary fibrosis. There was a trend toward lower exposure of nintedanib when it was added to pirfenidone.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease characterised by fibrosis of the lung alveoli and interstitium [1, 2]. Estimates of the worldwide prevalence of IPF range from two to 43 cases per 100000 people [2]. IPF has a poor prognosis [2] and there is a clinical need for novel therapies to improve outcomes in patients with IPF.

The pathogenesis of IPF is hypothesised to involve abnormal wound healing in response to epithelial injury [3]. The development of new treatments has focused on the signalling pathways involved in this response. Nintedanib (formerly known as BIBF 1120; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) is a potent intracellular inhibitor of tyrosine kinases that has been developed for the treatment of IPF and a number of cancer types. Nintedanib blocks the kinase activity of the platelet-derived growth factor, vascular endothelial growth factor and fibroblast growth factor receptors, all of which have been shown to be involved in the development of fibrosis [4, 5]. The results of the phase II To Improve Pulmonary Fibrosis with BIBF-1120 (TOMORROW) trial suggested that nintedanib 150 mg twice daily reduced decline in lung function in patients with IPF , with fewer acute exacerbations and preserved health-related quality of life [6]. Recently, the results of the two replicate phase III INPULSIS trials demonstrated that nintedanib reduced disease progression in patients with IPF by significantly reducing the rate of decline in forced vital capacity (FVC) [7]. In patients treated with nintedanib, the most common adverse events were gastrointestinal disorders, which accounted for the majority of discontinuations of study medication due to adverse eventss [7].

Pirfenidone (Shionogi & Co. (Osaka, Japan) and InterMune Inc. (Brisbane, CA, USA)) was approved for the treatment of IPF in Japan in 2008 (Shionogi & Co.) and for the treatment of adult patients with mild to moderate IPF in the European Union in 2011. In the phase III CAPACITY (Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes) 2 trial, 72 weeks' treatment with pirfenidone 2403 mg·day^{-1} significantly reduced the decline in percentage predicted FVC in patients with IPF *versus* placebo, but in the concurrent CAPACITY 1 trial, a significant difference from placebo was not observed [8]. Recently, the 52-week, phase III Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) trial demonstrated a benefit of pirfenidone *versus* placebo on change from baseline in percentage predicted FVC [9]. In a phase III study in Japanese patients with IPF, 52 weeks' treatment with pirfenidone 180 mg·day^{-1} significantly reduced the decline in vital capacity compared with placebo, with an adjusted mean change in vital capacity of -0.09 L with pirfenidone 180 mg·day^{-1} compared with -0.16 L with placebo [10]. Photosensitivity was the most frequent adverse event in the phase III study in Japanese patients, experienced by 51.4% of patients on pirfenidone 180 mg·day^{-1} *versus* 22.4% of patients on placebo [10]. However, in the international CAPACITY and ASCEND trials, the adverse event reported most frequently in patients treated with pirfenidone was nausea [8, 9]. A recent review of adverse events reported in patients treated with pirfenidone based on a data set with a cumulative total exposure of 2059 person-exposure years reported that nausea and vomiting were reported by 40% and 18%, respectively, of patients treated with pirfenidone [11].

There is some overlap in the adverse-event profiles of pirfenidone and nintedanib in patients with IPF in terms of gastrointestinal events and increases in liver enzymes [6–9]. However, pirfenidone and nintedanib have different metabolic profiles; pirfenidone is metabolised by various cytochrome P450 enzymes and predominantly excreted *via* the urine as the primary metabolite 5-carboxy-pirfenidone [12], whereas the metabolism of nintedanib is predominantly characterised by ester cleavage yielding BIBF 1202 ZW. BIBF 1202 ZW is subsequently glucuronidated by various uridine diphosphate glucuronosyltransferases (UGTs) in the intestine and by UGT1A1 in the liver to form BIBF 1202 glucuronide. Both nintedanib metabolites are excreted *via* the biliary system into the faeces [13].

This phase II study was conducted to determine the safety, tolerability and pharmacokinetics of nintedanib and its metabolites, alone and when added to ongoing pirfenidone therapy, in Japanese patients with IPF. The pharmacokinetics of pirfenidone (alone and when nintedanib was co-administered) were also investigated.

Materials and methods

Study subjects

Patients eligible for inclusion were aged ⩾40 years, with IPF diagnosed according to the American Thoracic Society/European Respiratory Society consensus statement [1] and the fourth version of the diagnostic guidelines for idiopathic interstitial pneumonia in Japan [14] <5 years before screening, and high-resolution computed tomography within 12 months of randomisation that was consistent with a diagnosis of IPF. Inclusion criteria included an FVC of ⩾50% of predicted value (according to the Japanese predicted normal equations) [15] and single-breath diffusing capacity for carbon monoxide

(D_{LCO}) of 30–79% of predicted value. Exclusion criteria included: elevated liver enzymes (>1.5 times the upper limit of the normal range); relevant airway obstruction; requirement for $\geq$15 h·day^{-1} supplemental oxygen; treatment with oral corticosteroids at unstable doses or in excess of the equivalent of prednisone 15 mg·day^{-1}, or with ketoconazole or atazanavir; an expectation of undergoing lung transplantation or of having rapidly deteriorating disease; or a life expectancy of <3 months from screening. Patients who had been receiving a steady dose of pirfenidone for $\geq$3 months were eligible for inclusion and were enrolled according to a pre-specified stratification scheme (described in the following section).

The trial was carried out in compliance with the Declaration of Helsinki (October 1996), and in accordance with the International Conference on Harmonisation Good Clinical Practice (GCP) guidelines and Japanese GCP regulations (Ministry of Health and Welfare Ordinance Number 28; March 27, 1997). All patients provided written informed consent before entering the study. The patients' safety was monitored by an independent data monitoring committee (IDMC). The trial was registered at www.clinicaltrials.gov with identifier number NCT01136174.

Study design

This study was a randomised, double-blind (with respect to nintedanib), placebo-controlled (within dose group), multicentre, dose-escalation trial. It consisted of a screening visit occurring 5–21 days before the start of treatment, a 14-day (cohorts 1 and 2) or 28-day (cohort 3) treatment period, an end-of-treatment visit 7 days after the last dose (or on premature treatment discontinuation) and a follow-up visit 3 weeks after the end-of-treatment visit (fig. 1). The treatment period included four (cohorts 1 and 2) or six (cohort 3) visits for pharmacokinetic sampling and safety assessments after the initiation of nintedanib treatment.

Patients were randomised to three cohorts using a stepwise approach, with IDMC safety review before transition to a higher dose group. Patients in cohort 1 were randomised to receive nintedanib 50 mg twice daily or placebo for 14 days; patients in cohort 2 were randomised to receive nintedanib 100 mg twice

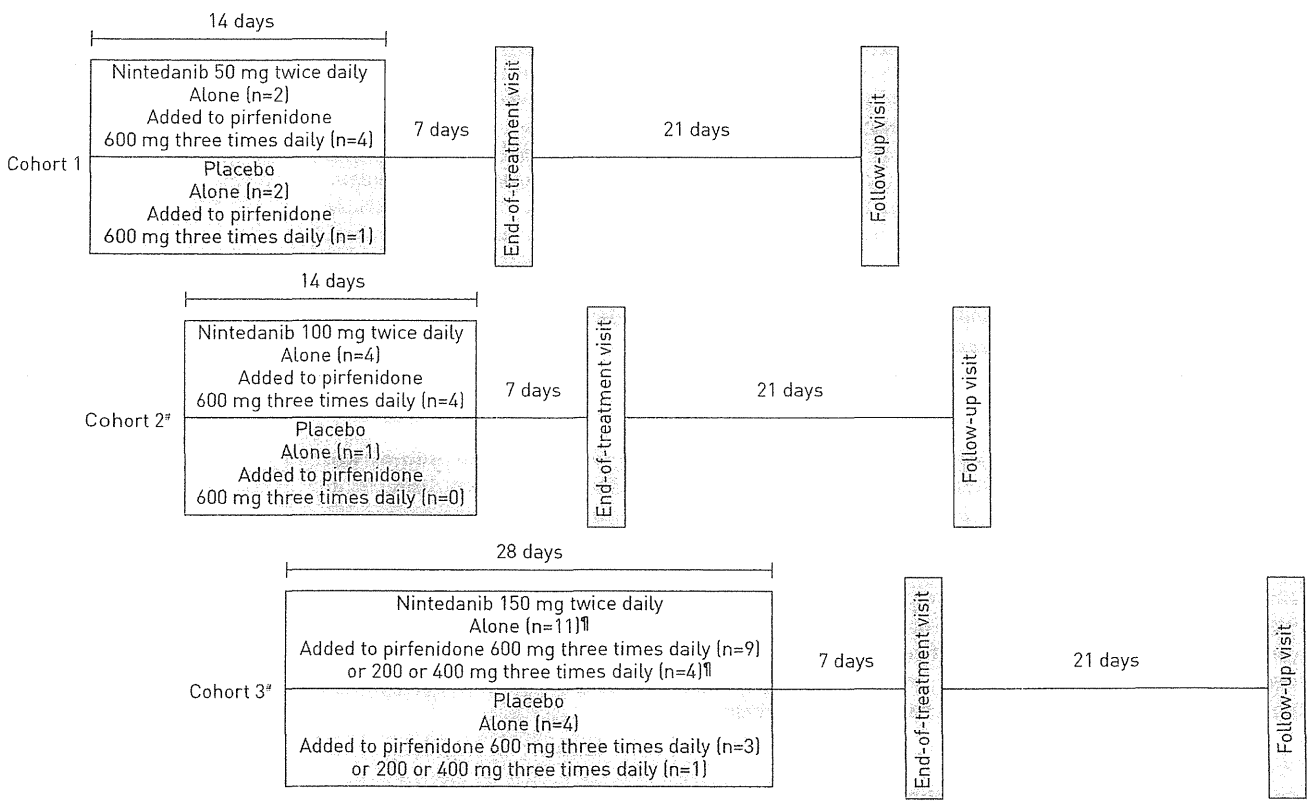

FIGURE 1 Study design and distribution of patients. #: patients' safety was reviewed by an independent data monitoring committee before patients were transitioned to these cohorts; ¶: two patients withdrew before study completion.

daily or placebo for 14 days; and patients in cohort 3 were randomised to nintedanib 150 mg twice daily or placebo for 28 days (fig. 1). Patients who had been receiving a steady dose of pirfenidone 600 mg three times daily for ≥3 months prior to inclusion were stratified to each cohort, and were included in the safety and pharmacokinetic analyses. Patients on a steady dose of pirfenidone 200 or 400 mg three times daily for ≥3 months prior to inclusion were allowed to participate in cohort 3 only and were included in safety analyses, but not in the pharmacokinetic analysis. It was planned that approximately half of every nintedanib and placebo group would be taking pirfenidone, except the placebo group in cohort 3, in which it was planned that two-thirds of the patients would be receiving pirfenidone. Pirfenidone was given as prescribed, after breakfast, lunch and dinner.

Safety analyses

All treated patients were included in the safety analyses. The safety end-points assessed were the incidence and intensity (mild, moderate or severe) of adverse events, withdrawal due to adverse events, routine laboratory tests, lung function measurements (FVC, forced expiratory volume in 1 s (FEV1) and D_{LCO}), blood pressure and pulse rate. Analyses of adverse events focused on treatment-emergent events, defined as those occurring up to 28 days after the completion of study medication, or starting before the first drug intake and deteriorating during treatment. Laboratory tests, lung function and vital signs were measured at screening, baseline, on days 2, 7 and 14 (plus days 21 and 28 for cohort 3) of treatment, and at the end-of-treatment visit. Safety results for patients receiving placebo with or without pirfenidone were grouped across all cohorts.

Pharmacokinetic analyses

For quantification of plasma concentrations of nintedanib, its metabolites (BIBF 1202 ZW and BIBF 1202 glucuronide) and pirfenidone, ~4 mL of venous blood was collected during study visits (pre-dose and at time-points from 30 min to 72 h after drug administration at steady state). Samples for pharmacokinetic assessment of pirfenidone were taken before and after the breakfast and lunch doses (pre-dose and at time-points from 30 min to 12 h after drug administration). Plasma concentrations of nintedanib, its metabolites and pirfenidone were determined using a validated liquid chromatography–tandem mass spectrometry assay (Nuvisan Pharma Services GmbH & Co. KG, Neu-Ulm, Germany).

The pharmacokinetic parameters calculated for nintedanib and pirfenidone included: the area under the concentration–time curve of the analyte in plasma at a steady state over a uniform dosing interval τ ($AUC_{\tau,ss}$) and over the time interval from t1 to t2 ($AUC_{t1-t2,ss}$); maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ ($C_{max,ss}$); time from dosing to maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ ($t_{max,ss}$); terminal half-life of the analyte in plasma at steady state ($t_{1/2,ss}$); apparent clearance of the analyte in plasma after extravascular administration at steady state ($CL/F_{,ss}$) (nintedanib only); apparent volume of distribution during the terminal phase λz following extravascular administration at steady state ($V_{z/F,ss}$) (nintedanib only); accumulation ratios based on $AUC_{t1-t2,ss}$ and $C_{max,ss}$ (nintedanib only); and ratios of $C_{max,ss}$ and $AUC_{t1-t2,ss}$ of the test treatment to the $C_{max,ss}$ and $AUC_{t1-t2,ss}$ of the reference treatment (pirfenidone only). Pharmacokinetics were assessed for nintedanib and its metabolites when it was given alone and when it was added to ongoing pirfenidone therapy (parallel-group comparison), and for pirfenidone with and without nintedanib co-administration (intra-individual comparison).

Results

Patients

A total of 66 patients were screened over eight sites, of whom 50 were randomised: six patients were randomised to receive nintedanib 50 mg twice daily, eight to nintedanib 100 mg twice daily, 24 to nintedanib 150 mg twice daily and 12 to placebo (fig. 1). At screening, 26 patients were being treated with pirfenidone, five of whom entered cohort 1 (four randomised to nintedanib 50 mg twice daily and one to placebo), four entered cohort 2 (all randomised to nintedanib 100 mg twice daily) and 17 entered cohort 3 (13 randomised to nintedanib 150 mg twice daily and four to placebo) (fig. 1). Of those randomised, 46 (92.0%) patients completed the study; four patients from the 150 mg twice daily group discontinued prematurely. There were no notable differences in baseline characteristics between groups (table 1). The mean age was 65.2 years and 70.0% of subjects were male. 10 patients were receiving systemic corticosteroids at baseline and four were receiving acetylcysteine.

Safety outcomes

Safety was assessed in all 50 randomised patients. A total of 23 (46.0%) patients experienced at least one adverse event: four (50.0%) patients receiving nintedanib 100 mg twice daily, 15 (62.5%) patients receiving nintedanib 150 mg twice daily and four (33.3%) patients receiving placebo (table 2). The adverse events were

TABLE 1 Baseline patient demographics and characteristics

	Placebo	Nintedanib 50 mg twice daily	Nintedanib 100 mg twice daily	Nintedanib 150 mg twice daily	Total
Subjects n	12	6	8	24	
Males	11 (91.7)	4 (66.7)	4 (50.0)	16 (66.7)	35 (70.0)
Age years	64.1±10.3	66.7±2.9	67.5±7.4	64.7±8.5	65.2±8.2
Height cm	166.2±7.0	159.3±7.2	158.3±7.5	159.5±7.8	160.9±7.9
Weight kg	69.1±12.1	58.6±7.5	63.9±9.7	62.1±13.2	63.6±12.1
Smoking status					
Ex-smokers	9 (75.0)	5 (83.3)	5 (62.5)	17 (70.8)	36 (72.0)
Never-smokers	3 (25.0)	1 (16.7)	3 (37.5)	7 (29.2)	14 (28.0)
FVC L	2.63±0.7	2.14±0.6	2.13±0.5	2.39±0.7	2.38±0.7
FVC % predicted	72.9±14.7	68.4±9.4	73.4±10.4	76.3±15.6	74.1±13.9
FEV1 L	2.22±0.6	1.85±0.5	1.72±0.4	1.98±0.5	1.98±0.5
D_{LCO} mL·min^{-1}·mmHg^{-1}	11.37±3.7	11.10±2.7	10.08±3.3	9.31±4.0	10.14±3.7
D_{LCO} % predicted	59.2±13.6	67.8±10.5	58.5±16.9	53.0±13.8	57.2±14.4
P_{aO_2} mmHg	76.73±8.0	77.67±7.1	83.24±19.9	84.08±12.8	81.41±12.8

Data are presented as n (%) or mean±SD, unless otherwise stated. FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension.

mild (87%) or moderate (13%) in intensity. The most common adverse events reported with nintedanib 150 mg twice daily were vomiting (five patients, all receiving nintedanib in addition to ongoing pirfenidone therapy) and nausea (five patients, four receiving nintedanib in addition to ongoing pirfenidone therapy). One serious adverse event (malignant hepatic neoplasm) was reported in the nintedanib 150 mg twice daily group during the follow-up period; this was not considered to be related to the study drug (previous computed tomography scans showed that the tumour was possibly present before study enrolment). Drug-related adverse events were reported by the investigator for 13 (26.0%) patients, most of which occurred in patients receiving nintedanib 150 mg twice daily (10 patients, seven receiving nintedanib in addition to ongoing pirfenidone therapy). The adverse events that led to discontinuation of study medication were increases in transaminase levels in three patients (all with nintedanib 150 mg twice daily, one with co-administration of pirfenidone 200 mg three times daily) and vomiting in one patient receiving nintedanib 150 mg twice daily and pirfenidone 200 mg three times daily. These adverse events resolved after treatment discontinuation. Photosensitivity was reported in one patient receiving pirfenidone alone and rash in one patient receiving pirfenidone with nintedanib 150 mg twice daily. FVC, FEV1 and D_{LCO} remained stable in all groups. There were no consistent changes in blood pressure or pulse rate and observed changes were not considered related to the study medication by the investigator.

Pharmacokinetic outcomes

After multiple dosing, maximum plasma concentrations of nintedanib were reached 2–4 h after dosing and a steady state was reached by day 7. Mean plasma concentrations of nintedanib after multiple dosing (day 14 for cohorts 1 and 2, day 28 for cohort 3) are shown in figure 2. For the 150 mg twice daily dose, mean plasma concentrations of nintedanib were lower when nintedanib was added to ongoing pirfenidone therapy, but high variability was observed.

After 28 days' treatment with nintedanib 150 mg twice daily, geometric means (gMean) of $C_{max,ss}$ and $AUC_{\tau,ss}$ of nintedanib were 41% lower (23.5 *versus* 39.7 ng·mL^{-1}) and 32% lower (149 *versus* 218 h·ng·mL^{-1}), respectively, when nintedanib was added to ongoing pirfenidone therapy, but the distribution of individual values overlapped (fig. 3). Values for gMean $t_{1/2,ss}$ and median $t_{max,ss}$ were similar when nintedanib was given alone as when given in addition to ongoing pirfenidone therapy (27.5 *versus* 28.4 h and 3.9 *versus* 3.9 h, respectively) (table 3). Mean $CL/F_{,ss}$ was 11 500 mL·min^{-1} in the absence of pirfenidone and 16 800 mL·min^{-1} when nintedanib was added to pirfenidone, and mean $V_{z/F,ss}$ was 27 300 L in the absence of pirfenidone and 41 200 L when added to ongoing pirfenidone (table 3). Mean R_A, AUC_{0-12} was 1.5 in the absence of pirfenidone and 1.7 when added to ongoing pirfenidone and mean R_A, C_{max} was 1.1 in the absence of pirfenidone and 1.3 when added to ongoing pirfenidone (table 3). Pirfenidone therapy had no effect on nintedanib accumulation ratios ($R_{A,C_{max}}$ and $R_{A,AUC_{0-12}}$) after multiple doses of nintedanib 150 mg twice daily (table 3). The effect of adding nintedanib to ongoing pirfenidone therapy on the pharmacokinetic parameters of nintedanib was similar for the nintedanib 100 mg twice daily dose as for the 150 mg twice daily dose (table 3). Measurements of pharmacokinetic

TABLE 2 Adverse events (AEs)

	Placebo[#]		Nintedanib 50 mg twice daily[¶]		Nintedanib 100 mg twice daily[+]		Nintedanib 150 mg twice daily[§]	
	Alone	Added to ongoing pirfenidone	Alone	Added to ongoing pirfenidone	Alone	Added to ongoing pirfenidone	Alone	Added to ongoing pirfenidone
Subjects n	7	5	2	4	4	4	11	13
Any AE	2 (28.6)	2 (40.0)	0	0	3 (75.0)	1 (25.0)	6 (54.5)	9 (69.2)
Serious AEs	0	0	0	0	0	0	1 (9.1)	0
Investigator-defined drug-related AEs	1 (14.3)	1 (20.0)	0	0	1 (25.0)	0	3 (27.3)	7 (53.8)
Most common AEs[f]								
Vomiting	0	0	0	0	0	0	0	5 (38.5)
Nausea	0	0	0	0	0	0	1 (9.1)	4 (30.8)
Diarrhoea	0	0	0	0	0	0	2 (18.2)	2 (15.4)
Nasopharyngitis	0	0	0	0	1 (25.0)	0	0	2 (15.4)
Abdominal discomfort	0	1 (20.0)	0	0	0	0	1 (9.1)	0
Stomatitis	0	0	0	0	1 (25.0)	0	0	1 (7.7)
Alanine aminotransferase increased[##]	0	0	0	0	0	0	2 (18.2)	0
Aspartate aminotransferase increased[##]	0	0	0	0	0	0	2 (18.2)	0
AEs leading to discontinuation of study drug	0	0	0	0	0	0	2 (18.2)	2 (15.4)
Transaminases increased	0	0	0	0	0	0	2 (18.2)	1 (7.7)
Vomiting	0	0	0	0	0	0	0	1 (7.7)

Data are presented as n (%) unless otherwise stated. "With pirfenidone" group included all pirfenidone doses. [#]: n=12; [¶]: n=6; [+]: n=8; [§]: n=24; [f]: reported in two or more patients; [##]: increases were reported based on the judgment of the investigator.

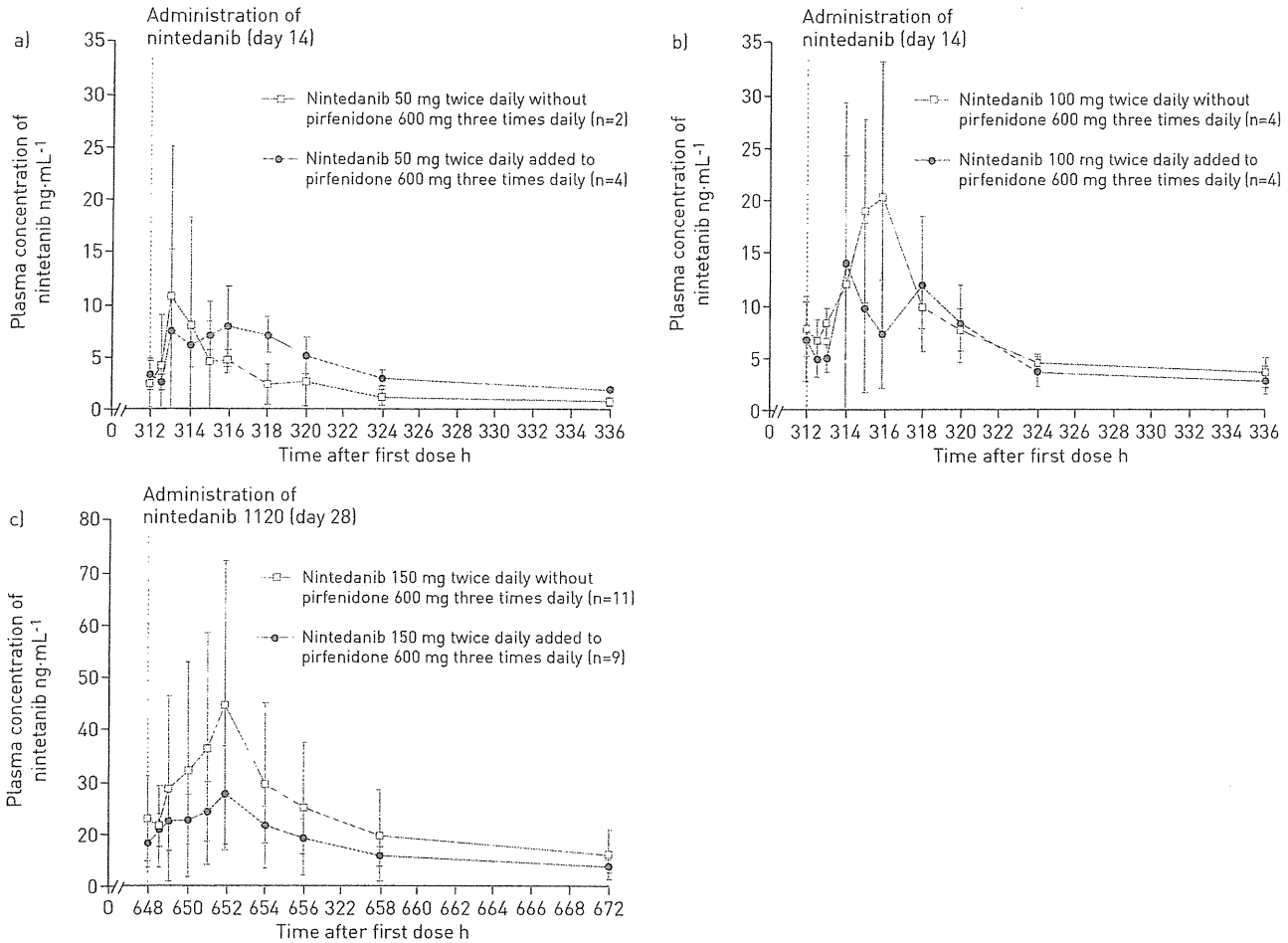

FIGURE 2 Arithmetic mean±SD plasma concentration–time profiles of nintedanib after a) multiple dosing of nintedanib 50 mg twice daily (day 14), b) 100 mg twice daily (day 14) and c) 150 mg twice daily (day 28) given alone and added to ongoing pirfenidone therapy (600 mg three times daily).

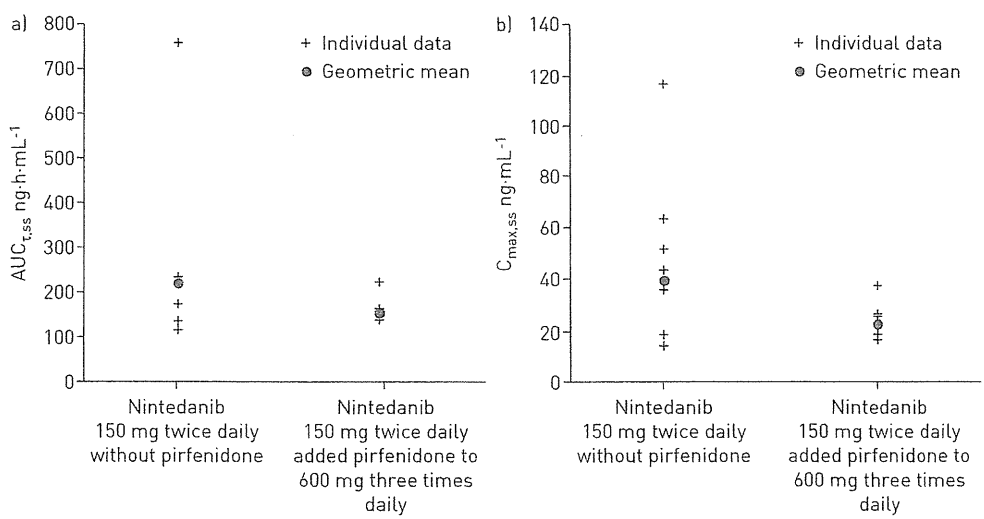

FIGURE 3 Individual and geometric mean area under the concentration–time curve of the analyte in plasma at a steady state over a uniform dosing interval τ ($AUC_{\tau,ss}$) and maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ ($C_{max,ss}$) values for nintedanib 150 mg twice daily given alone and added to ongoing pirfenidone therapy (600 mg three times daily).

TABLE 3 Pharmacokinetic parameters of nintedanib after multiple doses (steady state)

	Nintedanib 50 mg twice daily			Nintedanib 100 mg twice daily			Nintedanib 150 mg twice daily		
	Patients without/ with ongoing pirfenidone therapy	Alone	Added to ongoing pirfenidone 600 mg three times daily	Patients without/ with ongoing pirfenidone therapy	Alone	Added to ongoing pirfenidone 600 mg three times daily	Patients without/ with ongoing pirfenidone therapy	Alone	Added to ongoing pirfenidone 600 mg three times daily
$AUC_{\tau,ss}$ $h \cdot ng \cdot mL^{-1}$	2/4	33.7 (165)	67.9 (16.7)	4/3	115.0 (32.4)	86.0 (62.7)	9/7	218 (58.3)	149 (18.0)
$C_{max,ss}$ $ng \cdot mL^{-1}$	2/4	9.1 (173)	10.9 (50.3)	4/3	20.0 (64.5)	13.8 (113.0)	9/7	39.7 (68.1)	23.5 (27.2)
$t_{max,ss}$ h	2/4	2.4 (1.0–3.9)	3.9 (1.0–6.0)	4/3	3.4 (2.0–4.1)	2.0 (2.0–6.0)	9/7	3.9 (1.0–4.0)	3.9 (1.0–4.0)
$t_{1/2,ss}$ h	0/4	NA	25.4 (25.5)	4/3	23.4 (22.4)	30.5 (20.1)	9/7	27.5 (20.1)	28.4 (22.7)
$CL/F_{,ss}$ $mL \cdot min^{-1}$	2/4	24700 (165.0)	12300 (16.7)	4/3	14500 (32.4)	19400 (62.7)	9/7	11500 (58.3)	16800 (18.0)
$V_{z/F,ss}$ L	0/4	NA	27000 (39.5)	4/3	29300 (54.7)	51200 (76.7)	9/7	27300 (58.9)	41200 (33.8)
$R_{A,AUC_{0-12}}$	0/3	NA	2.2 (13.8)	4/3	2.0 (91.2)	1.5 (22.3)	9/6	1.5 (34.9)	1.7 (92.6)
$R_{A,C_{max}}$	2/4	2.3 (26.6)	1.9 (62.1)	4/3	1.5 (74.5)	1.4 (35.7)	9/6	1.1 (57.3)	1.3 (99.8)

Data are presented as n, geometric mean (geometric coefficient of variation %) or median (range). $AUC_{\tau,ss}$: area under the concentration–time curve of the analyte in plasma at a steady state over a uniform dosing interval τ; $C_{max,ss}$: maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ; $t_{max,ss}$: time from dosing to maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ; $t_{1/2,ss}$: terminal half-life of the analyte in plasma at steady state; $CL/F_{,ss}$: apparent clearance of the analyte in plasma after extravascular administration at steady state; $V_{z/F,ss}$: apparent volume of distribution during the terminal phase λz following extravascular administration at steady state; $R_{A,AUC_{0-12}}$: accumulation ratio based on $AUC_{0-12,ss}$; $R_{A,Cmax}$: accumulation ratio based on $C_{max,ss}$; NA: not applicable.

parameters were not obtained from enough patients receiving nintedanib 50 mg twice daily to adequately evaluate whether ongoing pirfenidone therapy had any effect.

After multiple doses of nintedanib alone, maximum plasma concentrations of the nintedanib metabolites BIBF 1202 ZW and BIBF 1202 glucuronide were reached 3–4 and 0.8–4.0 h, respectively, after drug administration, with gMean $t_{1/2,ss}$ values of approximately 23 and 46–56 h, respectively. When nintedanib was added to ongoing pirfenidone therapy, values for $t_{max,ss}$ were 3–5 and 0.7–8.0 h for BIBF 1202 ZW and BIBF 1202 glucuronide, respectively, while $t_{1/2,ss}$ was 27–26 h for BIBF 1202 ZW and 38–43 h for BIBF 1202 glucuronide. For the nintedanib 150 mg twice daily dose, gMean $C_{max,ss}$ was 51% lower (15.4 *versus* 33.2 ng·mL^{-1}) for BIBF 1202 ZW and 16% lower (107 *versus* 128 ng·mL^{-1}) for BIBF 1202 glucuronide when nintedanib was given in addition to ongoing pirfenidone therapy. $AUC_{\tau,ss}$ was 50% lower (118 *versus* 237 h·ng·mL^{-1}) for BIBF 1202 ZW and 20% lower (1100 *versus* 1380 h·ng·mL^{-1}) for BIBF 1202 glucuronide when nintedanib was given in addition to ongoing pirfenidone therapy. The effect of pirfenidone therapy on the pharmacokinetic parameters of BIBF 1202 ZW and BIBF 1202 glucuronide in the nintedanib 100 mg twice daily group was similar to that seen in the 150 mg twice daily group.

Maximum plasma concentrations of pirfenidone administered alone at the steady state were reached 1–1.6 h after the breakfast dose and 1–2 h after the lunch dose, with a gMean $t_{1/2,ss}$ of approximately 3–4 h (table 4). Plasma concentrations and pharmacokinetic parameters of pirfenidone were not affected by co-administration with nintedanib (table 4).

Discussion

The results of this study show that nintedanib 150 mg twice daily had an acceptable safety and tolerability profile in Japanese patients with IPF when given alone or when added to ongoing pirfenidone therapy, but with more reports of nausea and vomiting when nintedanib was added to ongoing pirfenidone than when given alone. All the adverse events reported in this trial were mild or moderate in intensity. The most common adverse events reported in patients receiving nintedanib were gastrointestinal side-effects, which were reported by approximately one-third of patients taking nintedanib alone or nintedanib in addition to already prescribed pirfenidone therapy. Nausea, vomiting and diarrhoea were reported only by patients in the nintedanib 150 mg twice daily group: five (20.8%) patients on this dose reported nausea, five (20.8%) patients reported vomiting and four (16.7%) patients reported diarrhoea. Gastrointestinal adverse events were not unexpected, as gastrointestinal side-effects have been observed in previous trials of nintedanib (at doses up to 150 mg twice daily) and pirfenidone (at doses up to 3600 mg·day^{-1}) in patients with IPF [6–9, 16], and in phase I and II studies of nintedanib at doses of 50 mg once daily to 300 mg twice daily in patients with advanced solid tumours and advanced non-small cell lung cancer [17, 18]. In this study, of the patients receiving nintedanib 150 mg twice daily in combination with pirfenidone, 69.2% reported adverse events, compared to 54.5% of patients receiving nintedanib 150 mg twice daily alone. The difference was mostly due to nausea (reported by four (30.8%) patients given nintedanib 150 mg twice daily in addition to pirfenidone and one (9.1%) patient given nintedanib 150 mg twice daily alone) and vomiting (reported by five (38.5%) of patients given nintedanib 150 mg twice daily in addition to pirfenidone and none given nintedanib alone); diarrhoea was not more frequently reported when nintedanib 150 mg twice daily was given in addition to pirfenidone than when it was given alone. Vomiting led to discontinuation of study medication in one patient (treated with nintedanib 150 mg twice daily in addition to pirfenidone 200 mg three times daily). Other adverse events associated with pirfenidone (but not nintedanib) include a dose-related increase in skin photosensitivity and rash [8, 11, 12]. The incidence of these adverse events did not increase when pirfenidone was co-administered with nintedanib in this study.

Increases in transaminase levels led to discontinuation of study medication in three patients (all treated with nintedanib 150 mg twice daily). The elevations in transaminases were reversible and resolved after treatment discontinuation. In a phase I study in Japanese patients with advanced solid tumours, liver enzyme elevations led to treatment discontinuation in three (25%) patients treated with nintedanib 200 mg twice daily [19]. In the phase II TOMORROW trial in patients with IPF, clinically significant elevations in liver enzyme levels were observed in six (7.1%) patients receiving nintedanib 150 mg twice daily [6]; these elevations were reversible. In the phase III INPULSIS trials, investigators were given recommendations for management of liver enzyme elevations through treatment interruption, dose reduction or treatment discontinuation. Across the two trials, elevations in liver transaminases (three or more times the upper limit of normal for aspartate aminotransferase or alanine aminotransferase) were observed in 5.0% of patients in the nintedanib groups and 0.7% of patients in the placebo groups. In general, elevations in liver enzymes returned to normal following treatment interruption, dose reduction or treatment discontinuation. There were no cases of Hy's law in patients treated with nintedanib [7].

TABLE 4 Pharmacokinetic parameters (steady state) of pirfenidone 600 mg three times daily

	Cohort 1			Cohort 2			Cohort 3		
	Patients without/ with ongoing pirfenidone therapy	Alone	With nintedanib 50 mg twice daily	Patients without/ with ongoing pirfenidone therapy	Alone	With nintedanib 100 mg twice daily	Patients without/ with ongoing pirfenidone therapy	Alone	With nintedanib 150 mg twice daily
After breakfast									
$AUC_{0-4,ss}$ h·ng·mL^{-1}	4/4	34400 (36.3)	34300 (39.9)	3/3	45800 (26.6)	35000 (32.2)	9/7	32500 (21.2)	35900 (21.8)
$C_{max,ss}$ ng·mL^{-1}	4/4	11900 (28.9)	12800 (44.3)	4/3	14600 (41.5)	15300 (51.1)	9/8	11200 (26.6)	12600 (27.2)
$t_{max,ss}$ h	4/4	1.6 (1.0–3.0)	0.7 (0.5–2.0)	4/3	1.5 (0.5–3.0)	2.0 (0.5–2.0)	9/8	1.1 (0.5–3.0)	0.8 (0.5–3.9)
$RAUC_{0-4,ss,T/R}$	0/4	1.0 (32.2)		0/2	0.7 (51.8)		0/7	1.1 (13.1)	
$RC_{max,ss,T/R}$	0/4	1.1 (45.1)		0/3	1.0 (38.6)		0/8	1.1 (12.4)	
After lunch									
$AUC_{0-8,ss}$ h·ng·mL^{-1}	4/4	72800 (40.7)	71000 (40.8)	3/3	84100 (11.4)	71500 (19.1)	8/6	60900 (22.9)	63600 (27.7)
$C_{max,ss}$ ng·mL^{-1}	4/4	14600 (20.9)	12000 (37.3)	4/3	15100 (19.5)	12100 (10.7)	9/8	12900 (30.2)	12500 (23.0)
$t_{max,ss}$ h	4/4	1.0 (0.5–3.1)	2.5 (1.0–3.9)	4/3	2.0 (1.0–3.0)	4.0 (2.0–4.0)	9/8	1.0 (0.4–6.0)	2.0 (0.5–4.4)
$t_{1/2,ss}$ h	4/3	3.4 (50.5)	4.0 (31.7)	4/1	3.5 (49.0)	3.6 (NC)	8/5	3.1 (40.6)	3.2 (39.1)
$RAUC_{0-8,ss,T/R}$	0/4	1.0 (4.7)		0/2	0.9 (21.2)		0/5	1.0 (14.6)	
$RC_{max,ss,T/R}$	0/4	0.8 (19.7)		0/3	0.8 (20.2)		0/8	0.9 (25.6)	
$AUC_{0-12,ss}$# h·ng·mL^{-1}	4/4	108000 (36.8)	105000 (40.3)	3/3	130000 (16.0)	107000 (22.4)	8/6	92000 (18.3)	102000 (22.2)
$RAUC_{0-12,ss,T/R}$	0/4	1.0 (9.9)		0/2	0.8 (30.8)		0/5	1.1 (12.2)	

Data are presented as n, geometric mean (geometric coefficient of variation %) or median (range). $AUC_{t1-t2,ss}$: area under the concentration–time curve of the analyte in plasma at a steady state over the time interval from t1 to t2; ; $C_{max,ss}$: maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ; $t_{max,ss}$: time from dosing to maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ; $RAUC_{t1-t2,SS,T/R}$: ratio of $AUC_{t1-t2,ss}$ of the test treatment to $AUC_{t1-t2,ss}$ of the reference treatment $RC_{max,ss,T/R}$: ratio of $C_{max,ss}$ of the test treatment to $C_{max,ss}$ of the reference treatment; $t_{1/2,ss}$: terminal half-life of the analyte in plasma at steady state. #: $AUC_{0-12,ss}$=$AUC_{0-4,ss}$ (post-dose after breakfast)+$AUC_{0-8,ss}$ (post-dose after lunch). NA: not applicable; NC: not calculated.