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R&D INSIGHT REPORT

Nintedanib: First Global Approval

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Abstract Nintedanib (Ofev®) is an orally available, small, multiple receptor tyrosine kinase inhibitor developed by Boehringer Ingelheim for the treatment of idiopathic pulmonary fibrosis (IPF) and cancer. Nintedanib received its first global approval in the US in October 2014 for the treatment of IPF. Nintedanib has received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use for the treatment of IPF, and for the second-line treatment in combination with docetaxel of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology. Phase 3 development programmes are also underway for colorectal cancer and ovarian cancer. Phase 2 investigation is being conducted for a variety of other solid tumours, including hepatocellular carcinoma, mesothelioma, prostate cancer, glioblastoma, renal cell carcinoma and endometrial cancer. This article summarizes the milestones in the development of nintedanib leading to this first approval for IPF.

This profile has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

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1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic lung disease of unknown aetiology, which has a poor long-term prognosis. The pathogenesis of the fibrosis appears to be influenced by multiple growth factors and signalling pathways that offer targets for intervention [1, 2].

Nintedanib (BIBF 1120), an indolinone derivative, is an intracellular tyrosine kinase inhibitor. It inhibits multiple kinases, including the vascular endothelial growth factor receptor (VEGFR) 1, 2 and 3, fibroblast growth factor receptor (FGFR) 1, 2 and 3, and platelet-derived growth factor receptor (PDGFR) α and β. Initially, it was developed as an antitumour agent to suppress tumour growth by preventing tumour angiogenesis, but it also provides clinical benefit in patients with IPF, since the receptors blocked by nintedanib have been shown to be involved in lung fibrosis [3].

Nintedanib (Ofev®) received its first global approval in the US at an oral dosage of 150 mg twice daily for the treatment of IPF on 15 October 2014 [4, 5]. The US approval was based on data from 1,231 patients participating in two identically designed phase 3 trials (INPULSIS®-1 and INPULSIS®-2) [6] and one phase 2 trial (TOMORROW) [7].

Oral nintedanib, under the trade name Vargatef®, received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use on 25 September 2014 for the treatment in combination with docetaxel of locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy [8]. Nintedanib (Ofev®) subsequently received a positive opinion from this committee for the treatment of

Features and properties of nintedanib

Alternative names	Ofev®; Vargatef®; BIBF 1120
Class	Acetamides, Esters, Indoles, Piperazines, Small-molecules
Mechanism of action	Platelet-derived growth factor (alpha and beta) receptor antagonists, Type 1, 2 and 3 fibroblast growth factor receptor antagonists, vascular endothelial growth factor receptor (1, 2 and 3) antagonists
Route of administration	Oral
Pharmacodynamics	Potently inhibits VEGFR-2, FGFR and PDGFR; demonstrates growth suppression and tumour regression in xenograft models
Pharmacokinetics	Dose-dependent C_{max} and AUC values; t_{max} 2–4 h; CL 83.4 L/h (adult); $t_{½}$ ≈12 h
Adverse events	
Most frequent	Diarrhoea, nausea, abdominal pain, elevated liver enzymes, vomiting, loss of appetite, weight loss, headache, hypertension
Occasional	Anorexia, asthenia, exanthema, fatigue
ATC codes	
WHO ATC code	L01X-E (protein kinase inhibitors), R07A-X (other respiratory system products)
EphMRA ATC code	L1X4 (antineoplastic protein kinase inhibitors), R7X (all other respiratory system products)
Chemical name	Methyl (3*Z*)-3-[({4-[*N*-methyl-2-(4-methylpiperazin-1-yl)acetamido]phenyl}amino)(phenyl)methylidene]-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylate

IPF on 20 November 2014. The product had been granted orphan drug status for this indication. Nintedanib has also been granted orphan drug status for IPF in Japan. Phase 3 development programmes are also underway for colorectal cancer and ovarian cancer. Phase 2 investigation is being conducted for a variety of other solid tumours, including hepatocellular carcinoma, mesothelioma, prostate cancer, renal cell carcinoma, glioblastoma multiforme and endometrial cancer.

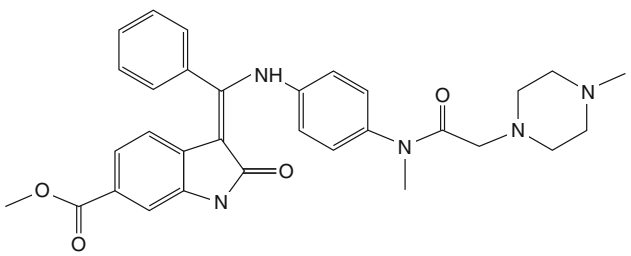
2 Scientific Summary

2.1 Pharmacodynamics

Nintedanib binds to the ATP binding site of the kinase domain of VEGFR-2, and displays inhibitory activity against a narrow range of kinases at pharmacologically relevant concentrations [9]. In vitro, the half-maximal inhibitory concentrations (IC_{50}) of nintedanib for susceptible human kinases were 13–34 nmol/L for VEGFR 1–3, 37–108 nmol/L for FGFR 1–3 and 59–65 nmol/L for PDGFR α and β [9]. The IC_{50} values for Lck, Flt-3, Src and Lyn were 16, 26, 156 and 195 nmol/L, respectively. Nintedanib inhibited the proliferation of VEGF-stimulated (EC_{50} 7–9 nmol/L) and FGF-stimulated (290 nmol/L) human endothelial cells (HUVEC), PDGF-stimulated pericytes (79 nmol/L) and vascular smooth muscle cells (69 nmol/L) [9]. VEGFR phosphorylation was inhibited for ≥32 h after the removal of nintedanib. In mouse xenograft models, nintedanib markedly inhibited tumour growth of human renal cell carcinoma, colorectal cancer, ovarian cancer, NSCLC and prostate carcinoma [9]. Nintedanib also demonstrated antitumour and antiangiogenic activity in animal models of lung cancer, pancreatic cancer, colorectal cancer and hepatocellular carcinoma in combination with standard chemotherapies, as well as in bevacizumab-resistant tumour models [10, 11].

In mouse models of bleomycin- or silica-induced pulmonary fibrosis, nintedanib reduced the level of fibrosis and decreased lung collagen [12]. In addition, nintedanib displayed anti-inflammatory activity, reducing lymphocyte and neutrophil counts, interleukin (IL)-1β and keratinocyte chemoattractant concentrations, and granuloma formation [12].

Nintedanib inhibited IL-1β-induced proliferation of normal human lung fibroblasts and lung fibroblasts from patients with IPF by 48 and 51 %, respectively, at a concentration of $1 \times 10^{-7.5}$ mol/L [13]. It also counteracted the profibrotic effects of transforming growth factor (TGF)-β1 (i.e. reduction of matrix metalloproteinase expression, enhanced collagen secretion and cell proliferation) on myofibroblasts from patients with IPF [14].



Chemical structure of nintedanib

In patients with advanced, refractory colorectal cancer treated with nintedanib once or twice daily for a median of four 28-day cycles, >60 % of patients had a ≥40 %

reduction in tumour blood flow and vascular permeability [15].

In patients with renal cell cancer, single-dose nintedanib 200 mg or nintedanib 200 mg twice daily for 15 days did not prolong the heart rate-corrected (Fridericia's method) QT interval [16].

2.2 Pharmacokinetics

The pharmacokinetics of nintedanib 150–250 mg twice daily in patients with NSCLC were described by a one-compartment model with first-order absorption and elimination rates [17], while a population pharmacokinetic model assumed a two-compartment model with first-order absorption and elimination rates to account for the observed delayed absorption [18]. The pharmacokinetics of nintedanib did not differ substantially between healthy volunteers and patients with IPF or cancer [5].

Oral nintedanib achieves maximum plasma concentrations (C_{max}) at a time (t_{max}) of 2–4 h after administration [5]. Nintedanib in plasma was highly bound to plasma proteins (97.8 %), predominantly albumin [5]. In patients with renal cell cancer administered nintedanib 200 mg twice daily, the C_{max} was 31.8 ng/mL after the first dose and 43.2 ng/mL on day 15 [16]. After administration of a 100 mg dose in healthy volunteers, the absolute bioavailability of nintedanib was 4.7 %. When administered after food, the area under the plasma concentration–time curve (AUC) increased by ≈20 % and the t_{max} was delayed by ≈2 h (from 2 to 4 h) compared with administration in the fasted state [5]. Over the dosage range 50–450 mg once daily or 150–300 mg twice daily, the AUC increased proportionately with the dose. The AUC in patients with IPF increased 1.76-fold with multiple administration and steady-state plasma concentrations were achieved within 1 week. In patients with NSCLC administered nintedanib 200 mg twice daily, the steady-state mean C_{max} was 50.4 ng/mL, the mean AUC_{24} was 308 ng·h/mL and the elimination half-life ($t_{½}$) was ≈12 h [19]. The apparent volume of distribution after intravenous administration was 1,050 L and the clearance was 1,390 mL/min [5].

Nintedanib is predominantly metabolized by hydrolytic cleavage to the free acid with subsequent glucuronidation by UGT1A1, UGT1A7, UGT1A8 and UGT1A10 [5]. Metabolism by cytochrome P450 (CYP) isoenzymes, mainly CYP3A4, plays a minor role [5]. In healthy volunteers, 93.4 % of a radiolabelled 100 mg dose of nintedanib was eliminated in the faeces, while renal excretion accounted to 0.65 % of the dose [20]. More than 90 % of the radioactivity was recovered by 4 days after administration [20].

In patients with IPF, mild [creatinine clearance (CrCl) 60–90 mL/min] or moderate (CrCl 30–60 mL/min) renal impairment did not affect nintedanib exposure, but experience with severe renal impairment (CrCl <30 mL/min) is limited [5]. While pharmacokinetic studies have not been conducted in patients with hepatic impairment, such impairment is expected to increase the plasma concentrations of nintedanib, since the drug is eliminated mainly by the biliary/faecal route.

Age, body weight and smoking affect nintedanib exposure, but not sufficiently to warrant dose adjustment [5].

2.2.1 Potential Drug Interactions

When administered concomitantly with pemetrexed [19] or carboplatin plus paclitaxel [21] in patients with NSCLC, or in combination with docetaxel to patients with prostate cancer [22], nintedanib did not significantly affect the pharmacokinetics of the other antitumour agents.

Concomitant administration of nintedanib and pirfenidone did not affect the exposure of pirfenidone, but did decrease the AUC and C_{max} of nintedanib to 68 and 59 %, respectively, in Japanese patients with IPF [5].

Nintedanib is a weak inhibitor in vitro of organic cation transporter-1 (OCT-1), breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp), and is a substrate of OCT-1, but these activities are not considered to be clinically relevant [5].

Since nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4, the AUC and C_{max} of nintedanib were increased 1.61- and 1.83-fold, respectively, when coadministered with the P-gp and CYP3A4 inhibitor ketoconazole, and the AUC and C_{max} were reduced to 50 and 60 %, respectively, when coadministered with the P-gp and CYP3A4 inducer rifampicin [5].

2.3 Therapeutic Trials

2.3.1 Idiopathic Pulmonary Fibrosis

Treatment of IPF with nintedanib significantly reduced the annual rate of decline in lung function, measured by forced vital capacity (FVC) [primary endpoint], by 52 % compared with placebo in the INPULSIS®-1 trial (−114.7 vs.−239.9 mL/year; $p < 0.001$) and by 45 % in the INPULSIS®-2 trial (−113.6 vs. −207.3 mL/year; $p < 0.001$) [6]. INPULSIS®-1 (NCT01335464) and INPULSIS®-2 (NCT01335477) were identically designed, randomized, double-blind, phase 3 trials in which patients, aged ≥40 years, with IPF diagnosed in the previous 5 years received treatment with oral nintedanib 150 mg twice daily ($n = 309$ and $n = 329$, respectively) or placebo ($n = 204$

and $n = 219$, respectively) for 52 weeks. At 52 weeks, the proportion of responders, defined as patients with an absolute decline in FVC % predicted of ≤5 %, was 52.8 and 53.2 % in the nintedanib arms (both $p = 0.001$), compared with 38.2 and 39.3 % in the placebo arms in INPULSIS®-1 and INPULSIS®-2, respectively [6].

There was no significant difference between nintedanib and placebo in the time to first investigator-reported acute exacerbation in INPULSIS®-1 [hazard ratio (HR) 1.15, 95 % CI 0.54–2.42; $p = 0.67$] or in the prespecified pooled analysis of both trials (HR 0.64, 95 % CI 0.39–1.05; $p = 0.08$), while the difference was significant in INPULSIS®-2 (HR 0.38, 95 % CI 0.19–0.77; $p = 0.005$) [6]. Similarly, there was no significant difference between nintedanib and placebo in the change from baseline in health-related quality of life (HR-QOL), as measured with the St. George's Respiratory Questionnaire (SGRQ), in INPULSIS®-1 (4.34 vs. 4.39 points; $p = 0.97$) or the pooled analysis of both trials (treatment difference −1.43 points; $p = 0.09$), while there was significantly less deterioration in HR-QOL with nintedanib compared with placebo (2.80 vs. 5.48 points; $p = 0.02$) in INPULSIS®-2 [6].

In the phase 2, TOMORROW trial (NCT00514683), nintedanib 150 mg twice daily reduced the annual rate of decline in FVC (primary endpoint) by 68.4 % compared with placebo (−0.06 vs. −0.19 L/year; $p = 0.06$ with the closed testing procedure for multiplicity), although the between-group difference did not reach statistical significance [7]. In this trial, patients aged ≥40 years with IPF diagnosed within the previous 5 years received treatment for 52 weeks with oral nintedanib 50 mg once daily ($n = 85$), nintedanib 50 ($n = 86$), 100 ($n = 85$) or 150 ($n = 84$) mg twice daily, or placebo ($n = 83$). The annual changes in FVC were −0.16, −0.21 and −0.17 L/year for nintedanib 100 mg twice daily, nintedanib 50 mg twice daily and nintedanib 50 mg once daily, respectively. Secondary endpoints supported the efficacy of nintedanib 150 mg twice daily. For instance, the proportion of patients with a >10 % reduction in FVC was significantly smaller with nintedanib 150 mg twice daily than with placebo (23.8 vs. 44.0 %; $p = 0.004$) and the mean absolute change from baseline in total lung capacity was significantly lower with nintedanib 150 mg twice daily than with placebo (0.12 vs. −0.24 L; $p < 0.001$) [7]. The incidence of acute exacerbations with nintedanib 150 mg twice daily was significantly lower than that with placebo (2.4 vs. 15.7 per 100 patient-years; $p = 0.02$). The mean absolute change from baseline in resting oxygen saturation was significantly less with nintedanib 150 mg twice daily than with placebo (−0.2 vs. −1.3 %; $p = 0.02$). SGRQ improved from baseline with nintedanib 150 mg twice daily compared with a deterioration in the placebo group (−0.66 vs. +5.46 points; $p = 0.007$) [7].

2.3.2 *Non-Small Cell Lung Cancer*

In the phase 3, LUME-Lung 1 trial (NCT00805194) assessing second-line treatment of NSCLC (all histologies), median independently-reviewed progression-free survival (PFS) [primary endpoint] at a median follow-up of 7.1 months was significantly greater with nintedanib plus docetaxel than with placebo plus docetaxel (3.4 vs. 2.7 months; $p = 0.0019$) [23]. The study enrolled patients with stage IIIB/IV recurrent NSCLC progressing after first-line chemotherapy who were randomized to receive intravenous docetaxel 75 mg/m^2 on day 1 plus oral nintedanib 200 mg twice daily ($n = 655$) or placebo ($n = 659$) on days 2–21 every 3 weeks. After a mean follow-up of 31.7 months, overall survival (OS), which was tested in a pre-specified stepwise order, was significantly longer with nintedanib than with placebo in patients with adenocarcinoma histology who had progressed within 9 months of the start of first-line therapy ($n = 405$) [10.9 vs. 7.9 months; $p = 0.0073$] and in all patients with adenocarcinoma histology ($n = 658$) [12.6 vs. 10.3 months; $p = 0.0359$], but did not differ significantly between nintedanib and placebo for the total population ($n = 1{,}314$) [10.1 vs. 9.1 months; $p = 0.2720$] or those with squamous cell histology ($n = 555$) [8.6 vs. 8.7 months; $p = 0.8907$] [23].

In the phase 3, LUME-Lung 2 trial (NCT00806819), which assessed second-line therapy with oral nintedanib 200 mg twice daily ($n = 353$) or placebo ($n = 360$), each in combination with pemetrexed (500 mg/m^2 intravenously every 21 days), in patients with advanced non-squamous NSCLC, the median centrally reviewed PFS (primary endpoint) was significantly higher with nintedanib than with placebo (4.4 vs. 3.6 months; $p = 0.04$) [24]. The addition of nintedanib to pemetrexed provided no survival benefit over pemetrexed alone. These are the results of a retrospective analysis in 713 patients of an intended 1,300 enrolled patients; further enrolment had been halted prematurely based on the recommendations of the Independent Data Monitoring Committee following a futility analysis of investigator-assessed PFS [25].

A phase 2 study demonstrated that nintedanib had single-agent activity in patients with an Eastern Cooperative Oncology Group (ECOG) criteria score of 0–2 with locally advanced or metastatic NSCLC ($n = 73$) [26]. All patients had previously received at least one line of platinum-based therapy. Patients were randomized to receive either oral nintedanib 150 mg ($n = 37$) or 250 mg ($n = 36$) twice daily. Median PFS for all patients was 6.9 weeks and did not differ between treatment groups, while median OS for all patients was 21.9 weeks. PFS and OS were longer in patients with ECOG 0–1 than in those with ECOG 2 ($n = 17$). Nearly one in two patients (46 %) experienced disease control (defined as complete response, partial

response or stable disease). Nintedanib showed a substantial clinical effect in the subset of 57 patients with 'good' performance status (ECOG 0-1); median PFS was 11.6 weeks, median OS was 37.7 weeks and the disease control rate was 59 % [26].

Several phase 1 studies have demonstrated that the maximum tolerated dose of nintedanib is 200 mg twice daily when administered in combination with docetaxel or pemetrexed in Caucasian or Japanese patients with advanced or recurrent NSCLC (where known: NCT00979576 and NCT00876460) [27–29].

2.3.3 Ovarian Cancer

In the randomized, double-blind, phase 3, LUME-Ovar 1 (AGO-OVAR 12) trial (NCT01015118) comparing oral nintedanib 200 mg twice daily with placebo (each added to standard chemotherapy consisting of carboplatin plus paclitaxel) as first-line therapy in patients ($n = 1{,}366$) with advanced ovarian cancer [Federation of Gynecology and Obstetrics (FIGO) Stages IIB–IV], the median investigator-assessed PFS (primary endpoint) was significantly greater with nintedanib than with placebo (17.3 vs. 16.6 months; HR 0.84, 95 % CI 0.72–0.98; $p = 0.024$) [30]. PFS values for nintedanib versus placebo obtained by independent central review (19.5 vs. 16.8 months; HR 0.86, 95 % CI 0.74–1.01) were similar to the investigator-assessed values, but the between-group difference did not reach statistical significance [31].

Results from a randomized, double-blind, phase 2 trial (NCT00710762) showed that maintenance nintedanib 250 mg twice daily was associated with a non-significant increase in the PFS rate at 36 weeks (primary endpoint) compared with placebo (16.3 vs 5.0 % of patients; HR 0.65; 95% CI 0.41–1.02; $p = 0.06$), in patients ($n = 83$) with relapsed ovarian cancer that had responded to prior chemotherapy [32]. OS did not differ between treatment groups (HR 0.84; 95 % CI 0.51–1.39).

A small phase 1 study ($n = 11$) [NCT01485874] found that the maximum tolerated dose of nintedanib was 100 mg twice daily when given in combination with pegylated liposomal doxorubicin to patients with platinum-resistant ovarian cancer [33].

2.3.4 Colorectal Cancer

In an open-label, phase 2 trial (NCT00801294) of monotherapy with alternating administration (7-day periods) of oral nintedanib 250 mg twice daily and afatinib 70 mg once daily in 46 patients with advanced pretreated colorectal cancer, the best response was stable disease observed in 20 patients (44 %) [34]. Seven patients (15.2 %) were progression-free at 16 weeks. Median PFS was 1.9 months and median OS was 5.5 months [34].

Oral nintedanib 150–200 mg twice daily showed similar efficacy to intravenous bevacizumab 5 mg/kg every other week as first-line therapy in combination with mFOLFOX6 (folinic acid + fluorouracil + oxaliplatin) in an open-label, randomized, phase 1/2 trial (NCT00904839) in 126 treated patients with metastatic colorectal cancer [35]. The median PFS (primary endpoint) was 10.6 months in both treatment arms. The confirmed overall response rate was 61 % for nintedanib and 54 % for bevacizumab, while the respective resection rates were 14 and 20 % [35].

2.3.5 Renal Cell Carcinoma

The efficacy of nintedanib and sunitinib were similar in a randomized, phase 2 study (NCT01024920) of first-line systemic therapy in patients with advanced renal cell carcinoma. The study compared oral nintedanib 200 mg twice daily with standard of care oral sunitinib (50 mg once daily given in repeated 6 week cycles: 4 weeks active, followed by 2 weeks rest). The median PFS was 8.4 months in each treatment arm and the median OS with nintedanib and sunitinib were 20.4 and 21.2 months, respectively [36].

2.3.6 Hepatocellular Carcinoma

Interim results of a randomized, phase 2 study (NCT00987935) of nintedanib 200 mg twice daily versus standard of care sorafenib (400 mg twice daily) in Asian patients with advanced hepatocellular carcinoma showed similar median time to progression (2.7 vs. 3.7 months) and median OS (10.7 vs. 9.5 months) in the two treatment arms [37].

An ongoing phase 1/2 study (NCT01004003) is evaluating nintedanib for the treatment of European patients with advanced hepatocellular carcinoma. The phase 1 part of the study determined the maximum tolerated dose of nintedanib to be 200 mg twice daily both in patients with AST and ALT $\leq 2 \times$ upper limit of normal (ULN) and Child-Pugh score 5–6 and in patients with AST or ALT >2 to $\leq 5 \times$ ULN, or Child-Pugh score 7 [38].This trial will enroll ≈ 115 patients in the UK/Europe.

2.3.7 Prostate Cancer

A phase 2 trial (EudraCT2005-002426-55) in patients ($n = 81$) with hormone-refractory prostate cancer, found no significant difference between oral nintedanib 150 and 250 mg twice daily in prostate specific antigen (PSA) response rate (proportion of patients with ≥ 20 % decline in PSA from baseline) [0 vs. 11 %] and median PFS (73.5 vs. 76.0 days) [39]. The rate of increase in PSA was

Key clinical trials of nintedanib (Boehringer Ingelheim)

Drugs(s)	Indication	Phase	Status	Location(s)	Identifier
Nintedanib	IPF	3	Completed	Multinational	NCT01335464 (INPULSIS®-1)
Nintedanib	IPF	3	Completed	Multinational	NCT01335477 (INPULSIS®-2)
Nintedanib	IPF	3 Ext	Active	Multinational	NCT01619085
Nintedanib	IPF	3	Recruiting	USA/Canada	NCT01979952
Nintedanib	IPF	2	Completed	Multinational	NCT00514683 (TOMORROW)
Nintedanib	IPF	2 Ext	Active	Multinational	NCT01170065
Nintedanib ± pirfenidone	IPF	2	Completed	Japan	NCT01136174
Nintedanib ± pirfenidone	IPF	2 Ext	Active	Japan	NCT01417156
Nintedanib + docetaxel	NSCLC	3	Completed	Multinational	NCT00805194 (LUME-Lung 1)
Nintedanib + pemetrexed	NSCLC	3	Active	Multinational	NCT00806819 (LUME-Lung 2)
Nintedanib + docetaxel	NSCLC	3	Recruiting	USA/Canada	NCT02231164 (LUME-Columbus)
Nintedanib	NSCLC	2	Completed	Germany	Reck et al. [26]
Nintedanib	NSCLC	2	Recruiting	USA	NCT01948141
Nintedanib + gemcitabine/ cisplatin	NSCLC	1/2	Active	UK/Europe	NCT01346540 (LUME-Lung 3)
Nintedanib + paclitaxel/ carboplatin	Ovarian cancer	3	Active	Multinational	NCT01015118 (LUME-Ovar 1)
Nintedanib	Ovarian cancer	2	Completed	UK	NCT00710762; EudraCT2005-002427-14
Nintedanib, cyclophosphamide	Ovarian cancer	2	Recruiting	UK	NCT01610869
Nintedanib, carboplatin/ paclitaxel	Ovarian cancer	2	Recruiting	France	NCT01583322
Nintedanib	Ovarian cancer/endometrial cancer	2	Recruiting	UK/Europe	EudraCT2013-002109-73
Nintedanib	Epithelial ovarian cancer	2	Recruiting	USA	NCT01669798
Nintedanib + BSC	Colorectal cancer	3	Recruiting	Multinational	NCT02149108; EudraCT2012-000095-42; LUME-Colon 1
Nintedanib, afatinib	Colorectal cancer	2	Completed	France	NCT00801294; EudraCT 2006-000893-56
Nintedanib, bevacizumab, mFOLFOX6	Colorectal cancer	2	Completed	Europe	NCT00904839; EudraCT 2008-005364-14
Nintedanib, afatinib, mFOLFOX7	Colorectal cancer	2	Active	Europe	EudraCT 2006-004528-35
Nintedanib	Prostate cancer	2	Completed	France	EudraCT 2005-002426-55; NCT02182063
Nintedanib, afatinib	Prostate cancer	2	Completed	UK	NCT00706628
Nintedanib, sorafenib	Hepatocellular carcinoma	2	Active	UK/Europe	NCT01004003; EudraCT 2009-011925-14
Nintedanib, sorafenib	Hepatocellular carcinoma	2	Active	Asia	NCT00987935
Nintedanib	Glioblastoma multiforme	2	Completed	USA	NCT01380782
Nintedanib	Glioblastoma multiforme	2	Completed	Denmark	NCT01251484
Nintedanib, docetaxel	Metastatic breast cancer	2	Recruiting	France	NCT01658462; EudraCT 2012-002214-38
Nintedanib	Oesophagogastric adenocarcinoma	2	Recruiting	USA	NCT02234596
Nintedanib, sunitinib	Renal cell carcinoma	2	Active	Multinational	NCT01024920; EudraCT 2009-009516-44
Nintedanib + carboplatin/ paclitaxel	Uterine cervical neoplasms	2	Recruiting	Belgium	NCT02009579
Nintedanib	Small cell lung cancer	2	Not yet recruiting	Canada	NCT02152059
Nintedanib	Thyroid cancer	2	Recruiting	Europe	NCT01788982; EudraCT 2012-004295-19
Nintedanib	Urothelial cancer	2	Not yet recruiting	Taiwan	NCT02278978
Nintedanib + pemetrexed/ cisplatin	Mesothelioma	2	Recruiting	Multinational	NCT01907100; EudraCT 2012-005201-48

BSC best supportive care, *Ext* extension study, *IPF* idiopathic pulmonary fibrosis, *NSCLC* non-small cell lung cancer

significantly ($p = 0.002$) slower in the nintedanib 250 mg arm compared with prior to treatment.

Nintedanib 250 mg twice daily ($n = 46$), afatinib 40 mg once daily ($n = 20$) and nintedanib plus afatinib combined [using either 70 ($n = 3$) or 40 ($n = 16$) mg of afatinib] each showed limited efficacy in a randomized, open-label, phase 2 trial (NCT00706628) in men with castration-resistant prostate cancer [40]. The progression-free rate at 12 weeks (primary endpoint) was 26 % for nintedanib and 0 % for both afatinib and the combination. The respective proportions of patients achieving a partial response or stable disease were 67, 38 and 29 %.

A phase 1 trial in 21 patients concluded that nintedanib could be safely administered at a dosage of 250 mg twice daily in combination with docetaxel 75 mg/m^2 in patients with advanced hormone-refractory prostate cancer, although based on the overall safety profile, 200 mg twice daily was the recommended dose for further study [41]. A disease response using PSA values and/or dimensional RECIST criteria was observed in 14 patients (73.7 %).

2.3.8 *Other Malignancies*

Phase 2 studies have also assessed the efficacy of oral nintedanib in the treatment of recurrent or persistent endometrial cancer (NCT01225887; recruitment suspended) [42], glioblastoma multiforme (NCT01251484 and NCT01380782) [43–45] and unresectable malignant pleural mesothelioma (NCT01907100; EudraCT 2012-005201-48) [46].

In addition, phase 1 trials have evaluated oral nintedanib in patients with multiple myeloma [47], early HER-2 negative breast cancer [48], gynaecological malignancies [49], acute myeloid leukaemia (NCT01488344) [50] and advanced solid tumours (including NCT01022853) [51–57].

2.4 Adverse Events

In the three pivotal placebo-controlled trials in patients with IPF (INPULSIS®-1, INPULSIS®-2 and TOMORROW), the most common adverse events with nintedanib 150 mg twice daily were gastrointestinal in nature [6, 7]. Increased liver transaminases were also common, but were reversible upon dosage reduction or discontinuation and did not have severe consequences [6, 7]. The most frequent adverse reactions with an incidence higher than with placebo across the three studies were diarrhoea (62 vs. 18 % with placebo), nausea (24 vs. 7 %), abdominal pain (15 vs. 6 %), elevated liver enzymes (14 vs. 3 %), vomiting (12 vs. 3 %), decreased appetite (11 vs. 5 %), headache (8 vs. 5 %), weight loss (10 vs. 3 %) and hypertension (5 vs. 4 %) [5]. Most adverse events were of mild or moderate severity [6]. Twenty one percent of nintedanib recipients, compared with 15 % of placebo recipients, discontinued therapy as a result of adverse events, most commonly because of diarrhoea (5 %), nausea (2 %) and decreased appetite (2 %) [5]. The most frequent serious adverse events with an incidence higher than with placebo were bronchitis (1.2 vs. 0.8 %) and myocardial infarction (1.5 vs. 0.4 %) [5]. Major adverse cardiovascular events (MACE) were reported in 0.6 % of nintedanib recipients compared with 1.8 % of placebo recipients [5].

Similar patterns of adverse events were observed in published phase 3 trials of nintedanib in oncology indications (NSCLC and ovarian cancer) [23, 30]. On the whole, treatment with nintedanib does not greatly increase the frequency of characteristic adverse events associated with VEGF inhibitors in the treatment of solid tumours. In-depth evaluation of the LUME-Lung 1 trial safety data showed that the overall antiangiogenic adverse event profile of nintedanib appears less pronounced than that described for other VEGF inhibitors in non-small cell lung cancer, especially in patients with squamous cell carcinoma [58].

The US prescribing information for nintedanib (Ofev®) in the treatment of IPF lists warnings or precautions for elevated liver enzymes, gastrointestinal disorders (diarrhoea, nausea and vomiting), embryofetal toxicity, arterial thromboembolic events, risk of bleeding and gastrointestinal perforation [5].

2.5 Ongoing Clinical Trials

A number of phase 2 or 3 clinical trials are ongoing or planned in IPF and various malignancies, as detailed below.

2.5.1 *Idiopathic Pulmonary Fibrosis*

A phase 3, multicentre, 12-month, randomized, double-blind, placebo-controlled trial of nintedanib 150 mg twice daily in patients with IPF (NCT01979952; planned enrolment 150), assessing IPF progression, was initiated by Boehringer Ingelheim in 2013.

In August 2014, Boehringer Ingelheim initiated a single-arm expanded access programme (EAP) in the US, to provide early access and to evaluate the safety and tolerability of nintedanib in patients with IPF (NCT02171156). The company will initiate an identical EAP in Brazil in November 2014 (NCT02230982).

Patients who completed the INPULSIS®-1 and -2 trials entered a phase 3 extension study (NCT01619085) to assess the long-term safety of nintedanib in patients with IPF.

Boehringer Ingelheim conducted a randomized, double-blind, placebo-controlled, phase 2 trial to assess the safety

and pharmacokinetics of rising doses of nintedanib, with or without pirfenidone, in Japanese patients with IPF (NCT01136174). The trial enrolled 50 patients and was completed in May 2011. A long-term follow-up trial, with an estimated enrolment of 20 patients, is ongoing, but no longer recruiting participants (NCT01417156).

Patients who completed the phase 2 TOMORROW trial (NCT00514683) could continue to receive nintedanib in an ongoing, phase 2, roll over study (NCT01170065).

2.5.2 Non-Small Cell Lung Cancer

In September 2014, Boehringer Ingelheim initiated a phase 3 clinical trial (NCT02231164; LUME-Columbus) to assess the safety and efficacy of nintedanib in combination with docetaxel in patients with advanced or recurrent NSCLC after failure of first-line platinum-based chemotherapy. This randomized, double-blind, placebo-controlled trial is intended to enrol 800 patients. Enrolment is underway in the US, and is expected to extend to additional countries.

In collaboration with Boehringer Ingelheim and the National Cancer Institute, the Roswell Park Cancer Institute initiated a single-group, phase 2 trial in January 2014 to evaluate nintedanib in the treatment of patients with advanced NSCLC who have failed up to two previous chemotherapy regimens (NCT01948141). The trial will enrol 67 patients.

In May 2011, Boehringer Ingelheim initiated the phase 1/2 LUME-Lung 3 trial in patients with NSCLC (NCT01346540). The run-in phase 1 portion is an open-label study to identify the maximum tolerated dose of nintedanib that can be added to standard first-line treatment with gemcitabine and cisplatin. The phase 2, placebo-controlled portion will assess the efficacy of nintedanib when added to gemcitabine and cisplatin therapy in patients with at least stable disease after two previous courses of the chemotherapy. The trial will enrol 165 patients in the UK.

In September 2014, the National Comprehensive Cancer Network awarded two grants to conduct clinical trials of nintedanib in patients with NSCLC. One of the grants was awarded for a pilot study of nintedanib in molecularly selected patients with advanced NSCLC to be conducted by Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. The other grant was for a randomized, phase 2 trial that will assess nintedanib versus placebo as prophylaxis against radiation pneumonitis in patients with unresectable NSCLC undergoing chemoradiation therapy. This trial will be conducted by Roswell Park Cancer Institute [59].

2.5.3 Ovarian and Endometrial Cancers

The NHS Greater Glasgow Health Board initiated a randomized, phase 2 trial (EudraCT2013-002109-73) in November 2013 to assess the efficacy, safety, tolerability and quality-of-life effects of nintedanib versus standard chemotherapy (paclitaxel plus doxorubicin liposomal plus topotecan, or carboplatin plus paclitaxel plus doxorubicin), in patients with relapsed or recurrent ovarian or endometrial cancer. The primary endpoint is PFS. The trial will enrol 120 patients who have previously received at least one prior platinum-containing regimen, in the UK/Europe.

University College, London, in collaboration with Boehringer Ingelheim is conducting the phase 2 METRO-BIBF trial (NCT01610869) to investigate the efficacy and tolerability of cyclophosphamide and nintedanib in patients with advanced ovarian cancer. The primary endpoint is OS. It will be assessed in year 3–4. Approximately 124 patients are expected to enrol in this trial in the UK.

Duke University, in collaboration with Boehringer Ingelheim is conducting a phase 2 trial (NCT01669798) to investigate the efficacy and tolerability of nintedanib in female patients with bevacizumab-resistant, persistent, or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. The primary endpoint is PFS, which will be assessed at 6 months. Approximately 56 patients are expected to be enrolled into this trial in the US.

A phase 2 study (NCT01583322) has been initiated to assess the efficacy of nintedanib as an alternative to bevacizumab in the neo-adjuvant setting during interval debulking surgery in patients with ovarian cancer. The trial will compare PFS and surgical complications of 188 patients with FIGO stage IIIC/IV disease treated first-line with either neo-adjuvant chemotherapy (carboplatin + paclitaxel) and interval debulking surgery or the same treatment + nintedanib.

2.5.4 Colorectal Cancer

In August 2014, Boehringer Ingelheim initiated a randomized, double-blind, phase 3 trial to investigate the efficacy of nintedanib versus placebo (both in combination with best supportive care) in patients with refractory, metastatic colorectal cancer (LUME-Colon 1; NCT02149108; EudraCT2012-000095-42). The co-primary endpoints are OS and PFS assessed over approximately 22 months. The global trial will enrol approximately 764 patients. Enrolment has begun in Portugal, Denmark, Belgium, Sweden, Austria, the UK, Luxembourg, Australia and Hong Kong. The first patient was enrolled in October 2014.

2.5.5 Other Malignancies

Phase 2 trials are also underway or planned in metastatic breast cancer (NCT01658462; EudraCT 2012-002214-38), oesophagogastric adenocarcinoma (NCT02234596),

uterine cervical neoplasms (NCT02009579), thyroid cancer (NCT01788982; EudraCT 2012-004295-19), small cell lung cancer (NCT02152059) and urothelial cancer (NCT02278978).

3 Current Status

Nintedanib received its first global approval on 15 October 2014 in the USA for the treatment of IPF [60]. It is the first tyrosine kinase inhibitor approved for this indication.

Nintedanib has received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use for the second-line treatment in combination with docetaxel of locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology, and separately for the treatment of IPF.

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