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A phase I study of nintedanib combined with cisplatin/gemcitabine as first-line therapy for advanced squamous non-small cell lung cancer (LUME-Lung 3)

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ABSTRACT

Background: There are limited treatment options for squamous non-small cell lung cancer (sqNSCLC) and prognosis remains poor. The safety and pharmacokinetics (PK) of nintedanib, a triple angiokinase inhibitor, plus cisplatin/gemcitabine as first-line treatment for advanced sqNSCLC patients, were evaluated.

Materials and methods: A phase I, dose-escalation study administering drugs in a 21-day cycle: cisplatin (75 mg/m^2, Day 1), gemcitabine (1250 mg/m^2, Days 1 and 8) and nintedanib (Days 2–7, 9–21) were given for 4–6 cycles, followed by monotherapy until disease progression or adverse events (AEs). Two nintedanib doses were tested, 150 mg twice daily (bid) and 200 mg bid, to determine maximum tolerated dose (MTD) based on occurrence of dose-limiting toxicities (DLTs) during Cycle 1. DLTs were primarily defined as drug-related non-hematologic (Grade ≥3) or hematologic (Grade 4) AEs.

Results: Sixteen patients were treated with nintedanib; n = 4 for 150 mg bid, n = 12 for 200 mg bid. No DLTs were observed in Cycle 1; therefore, the MTD was 200 mg bid. In subsequent cycles, two patients had DLTs: renal failure and reduced blood magnesium levels. The most common AEs were gastrointestinal. Three patients discontinued last study medication due to AEs and one had a nintedanib dose reduction. No relevant PK interactions were observed. Five patients had partial responses (31.3%) and eight had stable disease (50.0%); disease control rate was 81.3%. There were three long-term survivors (17–35 months).

Conclusions: The safety profile of nintedanib 200 mg bid plus cisplatin/gemcitabine was manageable, with AEs consistent with previous observations. PK data demonstrated no interaction, and preliminary antitumor activity was observed.

1. Introduction

Lung cancer is the most common cause of cancer mortality worldwide, with an estimated 1.6 million deaths annually [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of all newly diagnosed cases, with 30% of cases having squamous cell histology with 5-year survival rates below 5% [2,3]. Platinum-based chemotherapy in combination with paclitaxel, docetaxel, gemcitabine, or vinorelbine is recommended

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as the first-line treatment for patients with advanced or metastatic squamous NSCLC (sqNSCLC) [4,5], with necitumumab and pembrolizumab being recent addition to these options. Progress in the treatment of sqNSCLC has been slow, and this study was designed to assess the role of antiangiogenic therapy alongside standard therapy at a time when few therapeutic options existed.

Proangiogenic pathways are an essential feature of NSCLC and represent important therapeutic targets [6]. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), improved median overall survival (OS) and progression-free survival (PFS) when used as first-line combination therapy with platinum-based chemotherapy [7]. Bevacizumab is not recommended for the treatment of sqNSCLC as pulmonary hemorrhage in patients with squamous cell histology receiving bevacizumab (phase II study) and bleeding (Grade ≥3) rates of ~4% (phase III study) prompted the exclusion of this histological type from most NSCLC studies with bevacizumab [7,8].

In contrast, continued combination therapy with thalidomide and carboplatin/gemcitabine in selected patients with sqNSCLC (no progression after 2 cycles of treatment) showed PFS benefit [9]. This finding supported the current investigation of nintedanib in the treatment of sqNSCLC. Nintedanib is an oral, angiokinase inhibitor, targeting receptors in three proangiogenic pathways − VEGF receptors (VEGFRs), platelet-derived growth factor receptors α/β and fibroblast growth factor receptors (FGFRs) [10]. FGFRs could be relevant therapeutic targets as amplified FGFR1 occurs in ~20% of patients with sqNSCLC and may correlate with poor outcomes [3].

Nintedanib has a manageable safety profile in combination with docetaxel, pemetrexed and paclitaxel/carboplatin; [11] the maximum tolerated dose (MTD) with all combinations was defined at 200 mg twice daily (bid). The LUME-Lung 1 study evaluated nintedanib in combination with docetaxel after first-line treatment in patients with advanced NSCLC. Nintedanib/docetaxel significantly improved independently assessed PFS compared with placebo/docetaxel in the overall study population, and provided significant, clinically meaningful improvement in OS in patients with adenocarcinoma, in particular in patients with aggressive tumors [12]. Combination therapy was well tolerated, with a low frequency of fatal bleeding events (< 1.5%) [13]. Nintedanib in combination with docetaxel is approved in several countries, including the EU, for the treatment of locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumor histology after first-line chemotherapy [14]. The objective of this phase I study was to evaluate the safety, tolerability and pharmacokinetics (PK) of nintedanib in combination with cisplatin/gemcitabine as first-line treatment of patients with advanced sqNSCLC.

2. Materials and methods

2.1. Study design

This open-label, dose-escalation study evaluated drug-related dose-limiting toxicities (DLTs) and the safety and tolerability of nintedanib used in combination with cisplatin/gemcitabine in patients with Stage IIIB/IV sqNSCLC. The trial adhered to the principles of the Declaration of Helsinki; multicenter ethics approval was obtained and all patients provided written informed consent. This multicenter study was originally planned as a two-part, Phase I/II study in patients with sqNSCLC; however, the Phase II, double-blind, randomized, placebo-controlled portion of the study was not performed.

2.2. Patients and treatment

Eligible patients (inclusion/exclusion criteria listed in Supplementary table S1) received doses of 150 mg or 200 mg bid oral nintedanib, with intravenous cisplatin (75 mg/m^2 on Day 1 of each 21-day cycle) and gemcitabine (1250 mg/m^2 on Days 1 and 8 of each 21-day cycle), plus standard premedication for chemotherapy on Days 1 and 8. Nintedanib was administered from Day 2 of each cycle, with no intake on the days of chemotherapy (Days 1 and 8). The starting dose of nintedanib was 150 mg bid and, if no patients experienced a DLT during the first 21-day treatment cycle, the nintedanib dose was increased to 200 mg bid for the next cohort. If one patient experienced a DLT, a further three patients were to be recruited, increasing the cohort to six patients; if no further patient experienced a DLT at 150 mg bid, a further three patients were treated at 200 mg bid. If two or more of six patients treated at this dose level experienced a DLT, three additional patients were recruited to the lower-dose cohort. The MTD was defined as the dose of nintedanib added to cisplatin/gemcitabine at which no more than one out of six patients experienced a DLT during Cycle 1. Patients could receive 4–6 cycles of nintedanib in combination with cisplatin/gemcitabine, after which daily doses of nintedanib monotherapy were given until disease progression or the occurrence of an adverse event (AE) that contraindicated further treatment.

2.3. Assessments

2.3.1. Safety and tolerability

The primary endpoint was determination of the MTD based on the occurrence of DLTs during Cycle 1; the MTD was defined as the dose of nintedanib added to cisplatin/gemcitabine at which no more than one out of six patients experienced a drug-related DLT (or one dose tier below the dose at which two or more out of six patients experienced a drug-related DLT) during the first 21-day treatment cycle. The following drug-related AEs were classified as DLTs at any time, according to the Common Terminology Criteria for Adverse Events version 3.0: Grade ≥3 non-hematologic AEs, excluding transient electrolyte abnormality, hyperuricemia and isolated elevation of gamma-glutamyltransferase; gastrointestinal toxicity (e.g. nausea, vomiting, diarrhea, abdominal pain) or hypertension of Grade ≥3 despite optimal supportive care/intervention; Grade ≥3 alanine aminotransferase and/or aspartate aminotransferase elevation; and Grade 4 hematologic AEs, including neutropenia that was uncomplicated (not associated with fever ≥38.5 °C) for > 7 days (except for Cycle 1 where this definition did not apply), febrile neutropenia associated with fever ≥38.5 °C, and platelet decrease to Grade 4, or to Grade 3 associated with bleeding or requiring transfusions. Patient visits were scheduled for Days 1, 2, 8 (± 2 days), and 15 (± 2 days) during Cycles 1 and 2, Days 1 (± 2 days) and 8 (± 2 days) for Cycle 3 and in subsequent treatment cycles. Any DLTs experienced after the start of the second treatment period were considered separately from those in Cycle 1. All patients who received at least one dose of any study medication were included in the safety analysis. All AEs were recorded and safety was assessed from the occurrence of AEs and changes in laboratory parameters. Statistical methods were exploratory and descriptive. Analysis was performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC, US).

2.3.2. Efficacy

Objective response/best overall response and PFS were determined by investigator assessment (see Supplementary table S2).

2.3.3. PK

Blood samples for PK analyses were taken during Cycles 1 and 2 on Days 1 and 2 for cisplatin/gemcitabine, and on Day 2 only for evaluation of nintedanib and its major metabolites. Cisplatin/gemcitabine sampling was undertaken at 59 (immediately before the end of cisplatin infusion), 120, 240, and 360 min after the start of cisplatin infusion, and at 29 (immediately before the end of gemcitabine infusion), 50, and 90 min after the start of gemcitabine infusion. Nintedanib and metabolite sampling was undertaken prior to nintedanib administration and

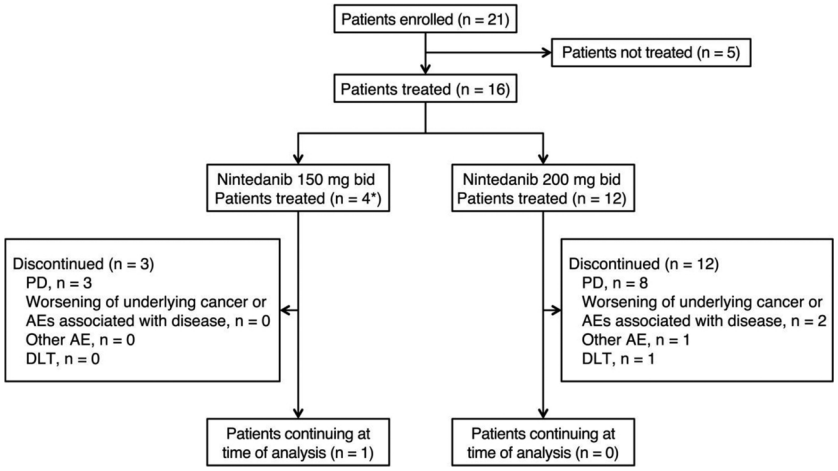

Fig. 1. LUME-Lung 3 patient enrolment and study design flow diagram.
*According to the 3 + 3 study design, only three patients should have been treated, but one additional patient was included in the 150 mg bid dose cohort because of an administrative error.
AE, adverse event; bid, twice daily; DLT, dose-limiting toxicity; PD, progressive disease.

1, 2, 4, 6, and 8 h post-administration. Plasma concentrations of nintedanib, its metabolites, and gemcitabine were analyzed using validated assays. Plasma concentrations of total and free platinum were analyzed by a validated mass spectrometry method. PK calculations were performed with WinNonlin® version 5.2 (Pharsight/Certara, Princeton, NJ, US).

3. Results

3.1. Patient population

Patients were recruited at six centers in the UK, Spain, The Netherlands and Italy, from February 2012 to June 2014. Twenty-one patients were enrolled, and 16 were subsequently treated (Fig. 1). Five patients were enrolled but not treated; one patient died prior to treatment initiation, one had an AE that prevented treatment, and three did not fulfil all of the inclusion criteria. Four patients were treated in the nintedanib 150 mg bid dose cohort; one extra patient being included in addition to the planned three patients because of an administrative error. Twelve patients were treated in the 200 mg bid dose cohort; demographic and clinical characteristics are shown in Table 1.

3.2. Treatment and dosing, DLTs and MTD

The median duration of nintedanib intake was 206 (range, 48–804) days in the 150 mg bid dose cohort and 100 (range, 5–264) days in the 200 mg bid dose cohort. Dose reduction was necessary in one patient in the 150 mg bid dose cohort (none in the 200 mg bid cohort). No DLTs were observed in Cycle 1 in either dose group; thus, the MTD was established as nintedanib 200 mg bid.

Three patients in the 150 mg bid dose cohort had Grade 3 or 4 hematologic toxicity during Cycle 1, an expected AE from cisplatin/gemcitabine treatment, and this was not classified as a DLT by the investigators. Cycle 1 toxicities resolved in all three patients following dose delay or reduction of gemcitabine alone, or both gemcitabine and cisplatin for Cycle 2; in subsequent cycles, one patient experienced recurrence of Grade 4 thrombocytopenia on two occasions, and another reported Grade 3 thrombocytopenia. No dose modifications were made for nintedanib in this group during Cycle 1 and no patients experienced a DLT after Cycle 1.

In the 200 mg bid dose cohort, one patient had Grade 4 neutropenia during Cycle 1; this event was not considered to be a DLT by the investigator. Of the 12 patients treated with 200 mg bid, two experienced DLTs after Cycle 1. One patient had renal failure (Grade 3) and was withdrawn from the study on Day 31. Investigator assessment suggested that renal failure was likely to be cisplatin-related, but a relationship to nintedanib could not be eliminated. In the other patient, Grade 3 hypomagnesemia persisting for 25 days was observed, and was considered to be drug-related. No action was taken and the patient recovered.

Table 1
Demographic and clinical characteristics – treated set.

	Nintedanib 150 mg bid (n = 4)	Nintedanib 200 mg bid (n = 12)	Total (N = 16)
Gender, n (%)			
Male	4 (100)	11 (91.7)	15 (93.8)
Female	0	1 (8.3)	1 (6.3)
Race, n (%)			
White	4 (100)	12 (100)	16 (100)
Smoking history, n (%)			
Ex-smoker	3 (75.0)	6 (50.0)	9 (56.3)
Current smoker	1 (25.0)	6 (50.0)	7 (43.8)
ECOG PS, n (%)			
0	2 (50.0)	3 (25.0)	5 (31.3)
1	2 (50.0)	9 (75.0)	11 (68.8)
Age, years			
Median (range)	61.0 (56–80)	65.0 (55–72)	64.5 (55–80)
Time from first diagnosis, months			
Median (range)[a]	0.99 (0.5–1.0)	0.89 (0.3–2.3)	0.92 (0.3–2.3)
Number of metastatic sites at screening[b]			
Median (range)	2.0 (1–3)	2.5 (1–4)	2.0 (1–4)
Patients with prior chemotherapy, n (%)	0	1[c] (8.3)	1 (6.3)

bid, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] Missing = 1.
[b] Documented by the investigator.
[c] One patient had received two courses of cisplatin as adjuvant chemotherapy 5 years prior to entering this study, which was not a protocol violation.

3.3. Adverse events

All 16 patients experienced at least one treatment-related AE (Table 2). Three patients, all in the 200 mg bid dose cohort, discontinued last study medication after the first treatment cycle. The reasons for discontinuation were dyspnea and dysphagia (considered unrelated to the study treatment), and renal failure (discussed above). Seven patients (43.8%) had serious AEs: two patients treated with nintedanib 150 mg bid, and five patients treated with nintedanib 200 mg bid. Two serious AEs were fatal (both in the 200 mg bid cohort), with the causes of death being dyspnea and sudden death. Both were considered to be related to underlying disease progression and not

Table 2
AEs by CTCAE grade preferred term and frequency and worst CTCAE based on laboratory values.

	Nintedanib 150 mg bid (n = 4)		Nintedanib 200 mg bid (n = 12)	
	All grades	Grade ≥3	All grades	Grade ≥3
Patients with any AE, n (%)	4 (100)	4 (100)	12 (100)	12 (100)
Patients with any drug-related AE; all courses, n (%)	4 (100)	4 (100)	12 (100)	11 (91.7)
Patients with DLT in Cycle 1, n (%)	0	0	0	0
Patients with any drug-related AE; Cycle 1, n (%)	4 (100)	3 (75.0)	10 (83.3)	5 (41.7)
Patients with any AE; Cycle 1, n (%)	4 (100)	3 (75.0)	10 (83.3)	5 (41.7)
Any AEs by worst CTCAE grade during Cycle 1 occurring at Grade ≥3				
Thrombocytopenia	3 (75.0)	3 (75.0)	2 (16.7)	0
Neutropenia	3 (75.0)	2 (50.0)	2 (16.7)	1 (8.3)
Decreased white blood cell count	0	0	2 (16.7)	1 (8.3)
Hypertension	0	0	2 (16.7)	1 (8.3)
Increased GGT	0	0	1 (8.3)	1 (8.3)
Decreased platelet count	0	0	1 (8.3)	1 (8.3)
Spontaneously reported AEs during on-treatment period, all courses[a]				
Nausea	4 (100)	0	9 (75.0)	0
Vomiting	2 (50.0)	0	8 (66.7)	0
Dyspepsia	2 (50.0)	0	0	0
Epistaxis	2 (50.0)	0	0	0
Diarrhea	4 (100)	1 (25.0)	5 (41.7)	0
Constipation	1 (25.0)	0	8 (66.7)	0
Decreased appetite	4 (100)	0	5 (41.7)	0
Dyspnea	3 (75.0)	0	5 (41.7)	2 (16.7)
Thrombocytopenia	3 (75.0)	3 (75.0)	4 (33.3)	0
Neutropenia	3 (75.0)	2 (50.0)	4 (33.3)	4 (33.3)
Asthenia	1 (25.0)	0	6 (50.0)	2 (16.7)
Cough	2 (50.0)	1 (25.0)	4 (33.3)	0
Weight decreased	2 (50.0)	0	4 (33.3)	0
Anemia	2 (50.0)	0	3 (25.0)	2 (16.7)
Rash	2 (50.0)	0	3 (25.0)	0
Alopecia	1 (25.0)	0	4 (33.3)	0
Insomnia	1 (25.0)	0	4 (33.3)	0
Hypertension	0	0	4 (33.3)	2 (16.7)
Arthralgia	1 (25.0)	0	2 (16.7)	1 (8.3)
Increased blood creatinine	0	0	3 (25.0)	1 (8.3)
Pruritis	2 (50.0)	0	1 (8.3)	0
Dizziness	2 (50.0)	0	1 (8.3)	0
Headache	2 (50.0)	0	1 (8.3)	0
Lower respiratory tract infection	2 (50.0)	1 (25.0)	1 (8.3)	0
Increased ALT	1 (25.0)	1 (25.0)	1 (8.3)	0
Decreased platelet count	0	0	2 (16.7)	1 (8.3)
Decreased white blood cell count	0	0	2 (16.7)	1 (8.3)
Hyponatremia	0	0	2 (16.7)	1 (8.3)
Increased blood uric acid	0	0	2 (16.7)	1 (8.3)
Increased GGT	0	0	2 (16.7)	1 (8.3)
Hypokalemia	0	0	1 (8.3)	1 (8.3)
Dysphagia	0	0	1 (8.3)	1 (8.3)
Fatigue	1 (25.0)	0	4 (33.3)	1 (8.3)
Pneumonia aspiration	0	0	1 (8.3)	1 (8.3)
Pneumonia	0	0	2 (16.7)	2 (16.7)
Hypomagnesemia	0	0	1 (8.3)	1 (8.3)
Renal failure	0	0	1 (8.3)	1 (8.3)
Lymphangiosis carcinomatosa	0	0	1 (8.3)	1 (8.3)
Sudden death	0	0	1 (8.3)	1 (8.3)
Worst CTCAE grade for AEs based on laboratory values during on treatment period				
Hemoglobin	4 (100.0)	0	12 (100.0)	1 (8.3)
White blood cell count	4 (100.0)	1 (25.0)	10 (83.3)	4 (33.3)
Platelets	4 (100.0)	3 (75.0)	11 (91.7)	2 (16.7)
Neutrophils	4 (100.0)	3 (75.0)	11 (91.7)	4 (33.3)

Percentages are calculated based on the total number of patients in each cohort. An individual patient could contribute to several items.
Elevations in hepatic enzymes were analyzed in more detail because of the known safety profile of nintedanib. One patient in the nintedanib 150 mg bid group had maximum ALT and AST values 3 x ULN and another patient in this group had ALT 5 x ULN. Three patients (75.0%) in the nintedanib 150 mg bid group and two patients (16.7%) in the 200 mg bid group had alkaline phosphatase levels > 1.5 x ULN. However, no patients had indications of drug-induced liver injury.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.
[a] AEs shown are those that occurred in > 25% of patients at any grade in either treatment arm or in at least one patient in either treatment arm at Grade ≥3.

study treatment. Common individual any-grade AEs were nausea, vomiting, constipation, decreased appetite, and diarrhea. The majority of hematologic AEs were reported during Cycle 1. A total of four patients had AEs that led to a dose reduction of cisplatin, gemcitabine or both. Only one patient had an AE that led to a dose reduction from nintedanib 150 mg to 100 mg.

As expected with cisplatin/gemcitabine treatment, the most common changes in laboratory parameters were the reduction in

Table 3
PK parameters for the nintedanib 200 mg bid (MTD) dose group by treatment cycle.

	Cycle 1			Cycle 2		
	Nintedanib	BIBF 1202	BIBF 1202 glucoronide	Nintedanib	BIBF 1202	BIBF 1202 glucoronide
$AUC_{0\text{-}12}$ (ng h/mL)						
gMean	167	248	–	228	253	2370
gCV (%)	73.0	183	–	105	118	72.4
C_{max} (ng/mL)						
gMean	23.6	24.1	15.2	34.4	34.3	177
gCV (%)	93.9	193	137	123	143	113
t_{max} (h)[a]						
Median	6.0	6.0	8.0	4.0	4.0	6.0
Range (%)	(1.0–8.0)	(2.0–8.0)	(6.0–8.0)	(2.0–6.0)	(4.0–8.00)	(0.0–8.0)

Note that extrapolation using λ_z was used to calculate $AUC_{0–12}$; nintedanib plasma was only sampled up to 8 h after drug intake, thus the corresponding plasma concentration–time profile does not cover the whole dosing interval of 12 h. Data shows parent compound and metabolites (BIBF 1202 and BIBF 1202 glucoronide). AUC, area under the curve; C_{max}, maximum plasma concentration; gCV, geometric coefficient of variation; gMean, geometric mean; MTD, maximum tolerated dose; PK, pharmacokinetics; t_{max}, time to maximum plasma concentration.
[a] Median and range.

platelets, hemoglobin, neutrophils and white blood cells (Table 2).

3.4. PK

Plasma concentrations of nintedanib peaked between 2 and 6 h after drug intake in most patients (Table 3). Nintedanib exposure was generally higher on Day 2 of Cycle 2 compared with the exposure observed after the first dose administration on Day 2 of Cycle 1, due to accumulation after repeated dosing (factor of approximately 2). These were not representative of steady-state values because the nintedanib dose on Day 1/Cycle 2 was omitted (steady state is reached after 1 week of continuous bid dosing). The variability of the PK parameters area under the curve (AUC) and maximum plasma concentration (C_{max}) was very high, with the coefficient of variation for geometric coefficient of variation values being in the range of 72.4–193% (Table 3). No terminal half-life ($t_{1/2}$) or related PK parameters were calculated for nintedanib due to the limited sampling duration (up to 8 h after drug administration). There were no substantive changes in key PK parameters of gemcitabine or cisplatin (AUC, $t_{1/2}$, C_{max}) in the presence of nintedanib (see Supplementary Fig. S1 and S2 and Table S3).

3.5. Efficacy

All patients were evaluated for response to treatment, five patients had a partial response (PR) and eight patients had stable disease (SD), giving an overall response rate of 31.3% (5/16) and a disease control rate of 81.3% (13/16) (Supplementary table S4). Median OS was 6.7 months (95% confidence interval [CI]: 4.4–not estimable; eight deaths). The 6-month OS rate was 69% (95% CI: 46–92). Median PFS was 4.2 months (95% CI: 2.6–6.0; 14 events) and the 6-month PFS rate was 25% (95% CI: 4–46%). There were three long-term survivors with survival (and best overall response) of 17 months (SD), 19 months (PR) and 35 months (SD), respectively, and a corresponding PFS of 6.0, 8.4 and 35.0 months; all responses were unconfirmed. One patient in the 150 mg bid cohort remains on treatment (57 months, as of November 2016).

4. Discussion

In patients with advanced sqNSCLC, nintedanib 200 mg bid combined with cisplatin/gemcitabine at standard doses has a tolerable safety profile with no DLTs observed in Cycle 1. A dose of nintedanib 200 mg bid is consistent with that used in other cancer studies [15–17].

Common AEs included hematologic and gastrointestinal toxicities. The hematologic AEs reported here are those commonly observed with cisplatin/gemcitabine, and the addition of nintedanib did not increase the toxicity rate [18]. The mild-to-moderate gastrointestinal AEs reported (including diarrhea) are similar to those seen with nintedanib monotherapy or in combination with chemotherapy [12,19]. Importantly, no unexpected AEs were reported and those commonly associated with other antiangiogenic agents, such as thromboembolic events, gastrointestinal perforation, and proteinuria, were not observed; [20] hypertension was reported in four patients, at Grade ≥3 in two patients. Importantly, there were no Grade ≥3 bleeding AEs in either dose group. These AEs were generally expected and manageable, and consistent with previous Phase I trials [21,22].

Nintedanib absorption after oral administration was rapid in combination with cisplatin/gemcitabine with comparable values to those previously reported with monotherapy [23]. The similarity of the PK data suggests that cisplatin/gemcitabine has no clinically relevant effect on the PK characteristics of nintedanib, whereas continuous treatment with nintedanib did not alter the PK parameters of cisplatin/gemcitabine. Total platinum exposure was slightly higher following repeated nintedanib dosing, possibly due to the long half-life and accumulation, but not due to any PK interaction [24,25]. Nintedanib and its metabolites do not interfere with cytochrome P450 (CYP450) enzymes, and drug–drug interactions due to CYP450 involvement are considered to be unlikely. This is an advantage because other agents used in combination with cisplatin/gemcitabine have the potential to be CYP450 substrates and/or inhibitors. Co-administration of nintedanib with cisplatin/gemcitabine is, therefore, a viable combination for future trials.

Initially, it was suspected that the strategy of combining antiangiogenic agents with chemotherapy would only benefit patients with non-squamous NSCLC, as patients with sqNSCLC faced increased bleeding risks. This study, combining a VEGFR inhibitor with cisplatin/gemcitabine for sqNSCLC, showed no serious bleeding events and contrasts with results for other small-molecule VEGFR inhibitors [26,27]. Although the number of patients treated in our study is small, the observed response rate seen with nintedanib and cisplatin/gemcitabine with three long-term survivors suggests promising clinical activity. Additionally, size is another limitation of the current study and, since the design of the LUME-Lung 3 study, the sqNSCLC treatment landscape has changed dramatically [4]. Necitumumab, in combination with cisplatin/gemcitabine, is recommended in European guidelines for the first-line treatment of epidermal growth factor receptor (EGFR)-expressing metastatic sqNSCLC [5]. More significantly, treatment of sqNSCLC can be addressed using therapies targeting programmed cell death-1 or programmed cell death-ligand 1 (PD-L1) [28–34]. Although not an optimal biomarker, measurement of PD-L1 expression is now recommended before first-line treatment in patients with metastatic NSCLC, including sqNSCLC [4]. In this respect, pembrolizumab, as monotherapy, is approved for the first-line treatment of metastatic

NSCLC in adults whose tumors express PD-L1 with a ≥50% tumor proportion score without EGFR or ALK tumor mutations [29,30]. Pembrolizumab has also been approved for the treatment of advanced or metastatic NSCLC in adults whose tumors express PD-L1 with a ≥1% tumor proportion score and who have received at least one prior chemotherapy regimen. The immunotherapy agents nivolumab and atezolizumab are indicated for the treatment of locally advanced or metastatic NSCLC for after platinum-based chemotherapy [28,31,33,35]. In combination with docetaxel, ramucirumab is also indicated for the treatment of locally advanced or metastatic sqNSCLC after platinum-based chemotherapy [31,33]. Given these developments, future clinical investigation of combination treatment with antiangiogenic agents and programmed death receptor-1 inhibitors may be warranted.

5. Conclusions

Continuous dosing of nintedanib 200 mg bid when combined with standard doses of cisplatin/gemcitabine shows a manageable safety profile in line with previous studies. PK data demonstrate no relevant interaction, and the combination showed antitumor activity in patients with sqNSCLC. These observations support further evaluation of this combination in trials. In addition, successful identification of predictive biomarkers could enable enrichment of the patient population, and increase the chance of finding a clinical benefit.

Congress presentations

This work was presented at the European Society for Medical Oncology, European Cancer Congress 2015, which was held in Vienna, Austria, 25–29 September 2015 (Forster et al. Nintedanib in combination with cisplatin/gemcitabine (CG) as 1st-line therapy for advanced squamous non-small cell lung cancer (sqNSCLC), Abstract/Poster number **P364**).

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This study was sponsored by Boehringer Ingelheim. Boehringer Ingelheim were involved in the study design, in the collection, analyses and interpretation of the data, and in the writing of and decision to submit this paper for publication.

Conflicts of interest

TDP and MC have nothing to disclose. MF has received a research grant and support for educational meetings from Boehringer Ingelheim. AH has taught at educational workshops (unrelated to this trial) organized by Boehringer Ingelheim. PG is a consultant to Roche, Eli Lilly, and Boehringer Ingelheim and participated in a speakers' bureau for Eli Lilly and Boehringer Ingelheim. YS has received research funding from AstraZeneca and, is a consultant to, and has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Boehringer Ingelheim. A-MCD is a consultant to Roche, Pfizer, AstraZeneca, Novartis, Eli Lilly, and Boehringer Ingelheim. MFn has received research funding and employment from MedImmune Ltd. DS, UvW, ABL, and RK are employees of Boehringer Ingelheim. RK has patents for Boehringer Ingelheim. SML is consultant to Roche, Pfizer, AstraZeneca, Novartis, and Bristol-Myers Squibb.

Contributors

Conception and design: Boehringer Ingelheim, SML, DS, UvW, A-BL, RK, MF, and AH. Data acquisition: MF, AH, TDP, MC, PG, YS, A-MCD, MFn, and SML. Data analysis: Boehringer Ingelheim and AH (progression-free survival and overall survival). Drafting and critically revising the manuscript, and final approval for publication: all authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2018.03.007.

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