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A phase II study of nintedanib in patients with relapsed small cell lung cancer

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ABSTRACT

Objectives: Nintedanib is an oral triple angiokinase inhibitor. This study was conducted to evaluate the efficacy and safety of nintedanib in patients (pts) with relapsed/refractory small cell lung cancer (SCLC).
Patients and methods: Pts with an ECOG PS from 0 to 2 who exhibited progression after one or two prior chemotherapy or chemo/radiotherapy were enrolled. Pts received nintedanib 200 mg BID daily in a 4-week cycle until progression or intolerable toxicity. The primary end point was the objective response rate (ORR). A two-stage design was employed. To continue to stage 2, ≥2 responders out of 22 pts were required.
Results: From Dec 2011 to June 2014, 24 pts were enrolled. Twenty-two pts completed treatment and were evaluable for response. The median follow-up was 9.7 (0.5–19.8) months. The median age was 64 (46–77) years. Twenty-two pts were male. Six pts had sensitive relapse. Eight pts received one prior chemotherapy. A median of one (range 1–5) cycle was administered. One pt had a partial response, and seven pts exhibited stable disease. The ORR was 5% (95% confidence interval [CI], 0.1–22.8). Median progression-free survival was 1.0 (95% CI, 0.9–1.1) month, and overall survival was 9.8 (95% CI, 8.4–11.2) months. The response criteria to proceed to full accrual were not met. The most frequent drug-related adverse events (AE) included hepatic enzyme elevation (86%), anemia (73%), anorexia (59%), and nausea (50%). Most AEs were mild and manageable. Grade 3 hepatic enzyme elevation occurred in 5 pts (23%).
Conclusions: Nintedanib exhibited only limited activity with a manageable AE profile in relapsed or refractory SCLC (NCT01441297).

1. Introduction

Despite a high initial response rate to chemotherapy, most patients with small cell lung cancer (SCLC) experience relapse within a year of completing first-line therapy and die from systemic metastases [1]. Although topotecan is regarded as the standard second-line therapy, the response rate is modest, and survival rates remain unsatisfactory [2,3]. Therefore, more effective novel agents are required for relapsed SCLC.

Human SCLC cells express functional vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3 and platelet-derived growth factor receptor (PDGFR)-β [4,5]. In addition, stem cell factor (SCF) and its receptor KIT are co-expressed in up to 70% of SCLC cell lines and clinical SCLC samples [6]. Therefore, we previously conducted a phase II study on sunitinib, a multi-target tyrosine kinase inhibitor that is effective against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR and KIT, in patients with relapsed or refractory SCLC. The response rate was 9% (2/23), and the disease control rate was 39% (9/23). However, most patients were unable to tolerate the sunitinib treatment due to significant toxicity, which resulted in frequent sunitinib dose interruptions. The actual dose intensity (the actual dose delivered as a proportion of the planned dose with or without delay) of sunitinib was 69.7%, which may have led to the relatively low efficacy [7]. In contrast, a recent randomized phase II trial demonstrated that maintenance sunitinib after chemotherapy improved progression-free survival (PFS) in untreated patients with extensive-disease (ED)-SCLC. In addition, the overall survival (OS) was promising despite the cross-over design. These findings suggest that multi-targeted VEGFR inhibitors may be effective against SCLC [8].

Nintedanib is a potent, oral angiokinase inhibitor that targets the pro-angiogenic pathways mediated by VEGFR1-3, fibroblast growth factor receptor (FGFR) 1-3, and PDGFR α and β [9]. *FGFR1* is amplified in 6% of SCLC, and sensitivity to FGFR inhibitors has

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Table 1
Baseline characteristics of patients.

Characteristics		Patient No.
Age, years	Median (range)	64 (46–77)
Gender	Male	22
	Female	2
ECOG PS	0	1
	1	11
	2	12
Smoking	Median (range), pack-year	39 (11–94)
	Ever	21
	Never	3
Prior therapy No	One	8
	Two	16
Relapse pattern	Sensitive	6
	Resistant or refractory	18

been described in some, but not all, SCLC [10]. Recently, a randomized phase III study demonstrated a survival benefit of nintedanib in combination with docetaxel versus docetaxel alone in previously treated lung adenocarcinoma. In addition, nintedanib alone exhibited a manageable toxicity profile in phase I/II trials [11,12]. Given the potential activity through the inhibition of angiogenesis and a favorable toxicity profile, we conducted a phase II study of nintedanib in patients with relapsed or refractory SCLC.

2. Patients and methods

2.1. Eligibility criteria

Patients with ED-SCLC who progressed during or after treatment with at least one platinum-based chemotherapy were eligible for inclusion in the study. Patients, who have relapsed beyond 3 months of completing first-line treatment, were considered as the sensitive relapse. Patients who have progressed within 3 months were considered as the refractory relapse. Patients, who did not respond or relapsed during first-line treatment, were considered as resistant [13]. All patients displayed measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of less than or equal to 2, adequate hepatic, renal and hematologic function, and normal thyroid function. Additionally, all patients were at least 18 years of age. Patients were excluded if they presented a grade 3 hemorrhage based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) or gross hemoptysis (>5 mL of blood per episode and >10 mL of blood/d) less than 4 weeks prior to the onset of treatment. Prior treatment with anti-angiogenic agents was not permitted. Additional exclusion criteria included the following: uncontrolled hypertension; a diagnosis of any second malignancy within the preceding 3 years (except for adequately treated basal cell or squamous cell skin cancer or in situ carcinoma of the cervix uteri); a history of or current brain metastases, spinal cord compression, carcinomatous meningitis or evidence of brain or leptomeningeal disease; clinically significant cardiovascular disease (severe/unstable angina, myocardial infarction, coronary artery bypass graft, or symptomatic congestive heart failure); pulmonary embolism or cerebrovascular accident within the 12 months prior to the study drug administration; a history of a decline in the left ventricular ejection fraction below the lower limit of normal or ongoing cardiac dysrhythmias (NCI CTCAE grade $\geq$2), and atrial fibrillation or prolongation of the QTc interval. All patients with reproductive potential were required to use contraception during treatment. All patients were required to provide written informed consent prior to entry into the study.

Table 2
Adverse events.

	Grade 1	Grade 2	Grade 3	Grade 4
	N (%)	N (%)	N (%)	N (%)
Hematologic				
Anemia	12 (50)	6 (25)	0 (0)	0 (0)
Thrombocytopenia	6 (25)	0 (0)	0 (0)	0 (0)
Leukopenia	5 (21)	0 (0)	0 (0)	0 (0)
Neutropenia	0 (0)	2 (8)	1 (4)	0 (0)
Non-hematologic				
ALT elevation	5 (21)	9 (38)	5 (21)	0 (0)
AST elevation	5 (21)	9 (38)	2 (8)	0 (0)
Anorexia	6 (25)	7 (29)	0 (0)	0 (0)
Fatigue	7 (29)	5 (21)	1 (4)	0 (0)
Nausea	7 (29)	5 (21)	0 (0)	0 (0)
Diarrhea	8 (33)	1 (4)	0 (0)	0 (0)
Pain	4 (17)	5 (21)	0 (0)	0 (0)
Vomiting	5 (21)	1 (4)	0 (0)	0 (0)
Constipation	5 (21)	1 (4)	0 (0)	0 (0)
Abdominal pain	4 (17)	1 (4)	0 (0)	0 (0)
Epigastric soreness	3 (12)	3 (12)	0 (0)	0 (0)
Myalgia	2 (8)	2 (8)	0 (0)	0 (0)
Dyspepsia	3 (12)	0 (0)	0 (0)	0 (0)
Rash	2 (8)	1 (4)	0 (0)	0 (0)
Headache	2 (8)	1 (4)	0 (0)	0 (0)
Neuropathy-sensory	0	1 (4)	0 (0)	0 (0)
Mucositis	1 (4)	0 (0)	0 (0)	0 (0)
Dry mouth	1 (4)	0 (0)	0 (0)	0 (0)
Hand-foot syndrome	1 (4)	0 (0)	0 (0)	0 (0)
Hyponatremia	1 (4)	0 (0)	0 (0)	0 (0)
Hyperglycemia	1 (4)	0 (0)	0 (0)	0 (0)

2.2. Study design

This was an open-label, single-arm, phase II study conducted at a single center (National Cancer Center, Goyang, Korea). The primary end point was the objective response rate (ORR), defined as the percentage of all patients who experienced a confirmed complete response or partial response (PR) based on RECIST1.1 [14]. The secondary end points included safety and tolerability, PFS and OS. The protocol was approved by an independent ethics committee/institutional review board and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice.

2.3. Study treatment

The patients received nintedanib 200 mg orally twice daily every 4 weeks. In the case of treatment-related adverse events, nintedanib dose reductions were performed accordingly by 25% for each additional toxicity grade (i.e., 25% for grade 2 and 50% for grade 3 toxicity). Treatment was continued until tumor progression, withdrawal of consent or unacceptable toxicity, defined as grade 4 hematologic toxicity and grade $\geq$ 3 non-hematologic toxicity inducing a persistent delay in administration of the next cycle beyond day 42 of each cycle.

2.4. Assessment

The baseline evaluations included medical history, physical examination, tumor imaging with computed tomography or a magnetic resonance imaging scan, laboratory tests (hematology, urinalysis, coagulation, blood chemistry and pregnancy tests), three 12-lead electrocardiogram (ECGs) and echocardiography. Hematology, blood chemistry and thyroid function (T3, thyroid-stimulating hormone (TSH), and free T4) evaluations were performed before each treatment cycle. The response assessment was performed at the end of dosing in cycles 1 and 2 followed by every two cycles according to the RECIST criteria 1.1. Initially, tumor responses were evaluated by the investigator. Subsequent to the evaluation