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ORIGINAL ARTICLE

Phase II study of motesanib in Japanese patients with advanced gastrointestinal stromal tumors with prior exposure to imatinib mesylate

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Abstract

Purpose Motesanib (AMG 706) is a multitargeted anticancer agent with an inhibitory action on the human vascular endothelial growth factor receptor, the platelet-derived growth factor receptor, and the cellular stem-cell factor receptor (KIT). The aim of this single-arm phase II clinical study was to assess the efficacy and safety of single-agent motesanib in Japanese patients with advanced gastrointestinal stromal tumors with prior exposure to imatinib mesylate.

Methods All patients had experienced progression or relapse while undergoing with imatinib as 400 mg/day or higher. The patients were administered 125 mg of motesanib once daily. The primary endpoint was overall response. Efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumor, and safety was assessed according to the Common Terminology Criteria for Adverse Events (version 3).

Results Of 35 enrolled and treated patients, no patient showed a complete response, and one patient showed a partial response (PR). Seven had stable disease (SD) for at least 24 months, two of whom continued to have SD for more than 2 years. The median progression-free survival time was 16.1 weeks. Motesanib was well tolerated; commonly reported treatment-related adverse events were hypertension, diarrhea, and fatigue. Anemia was the only hematological toxicity that was reported.

Conclusions One patient showed PR, and seven patients showed SD more than 24 weeks. Motesanib was found to be safe and well tolerated. The observed toxicities were consistent with Phase I study findings.

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Keywords Motesanib · Angiogenesis inhibitor · Gastrointestinal stromal tumor (GIST)

Introduction

Gastrointestinal stromal tumor (GIST) is a rare stromal neoplasm that predominantly arises from the muscularis propria layers, representing the most common mesenchymal tumor of the gastrointestinal tract. Although the primary therapy for nonmetastatic GIST is surgical resection, there still remain unresectable cases of advanced or metastatic GIST. Unresectable GISTs are resistant to conventional chemotherapy and radiotherapy [1]. Before imatinib mesylate was introduced in clinical practice, the prognosis for patients with unresectable GIST was dismal, with a median survival period of 22 months [2].

The critical transforming and oncogenic mechanisms of GISTs are activating mutations in the stem-cell factor receptor, KIT tyrosine kinase [3]. About 5% of GISTs are caused by activating mutations of the platelet-derived growth factor receptor alpha (PDGFRA), and are independent of *c-kit* mutations [4]. The *c-kit* and PDGFRA mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GIST.

Imatinib mesylate blocks the constitutively activated form of KIT in GISTs, and has dramatically improved the outcome for patients with unresectable GIST [5]. Treatment with imatinib mesylate results in partial response (PR) or stable disease (SD) in approximately 80% of patients with advanced or metastatic GIST [6], and the 2-year survival rate of these patients is reported to be 70% [7].

However, approximately 10–15% of advanced GIST patients will suffer a progressive disease (PD) despite treatment with imatinib mesylate. Many of the patients who initially responded to imatinib mesylate therapy experience tumor progression after an average of 2 years of treatment [7, 8].

Sunitinib is an orally administered receptor tyrosine kinase (RET) inhibitor that targets multiple kinases and is used as a second-line treatment for patients with imatinib-resistant or -intolerant GIST. A Phase III double-blind, placebo-controlled trial comparing sunitinib with placebo showed that the time to progression was significantly longer in the sunitinib group than in the placebo group (6.3 versus 1.5 months). Adverse reactions, though observed, were acceptable [9]. However, despite initial response or stabilization, the disease developed resistance in most patients after approximately 7 months. Because no therapies are available for patients with GIST once imatinib and sunitinib fail, there exists a need for alternative agents that block the signaling pathways in GIST cells.

Motesanib is a novel, synthetic, small molecule that strongly and selectively inhibits vascular endothelial growth factor receptors 1, 2, and 3, as well as the cellular KIT, the platelet-derived growth factor receptor (PDGFR), and the glial-derived nerve growth factor family ligand RET. The safety and pharmacokinetic (PK) profile of motesanib were evaluated in a Phase I, monotherapy, open-label, dose-finding study [10]. In this study, motesanib showed clinical activity in patients with advanced refractory solid tumors; SD was observed in a significant proportion of the patients, although the overall tumor response rate was low.

The above findings prompted us to conduct a Phase II study to evaluate the efficacy, safety, and PK of motesanib in Japanese patients with advanced GIST, after failure or withdrawal of imatinib mesylate due to resistance or intolerance.

Materials and methods

Patients

Japanese patients with pathologically confirmed advanced or metastatic GIST were eligible for this study if they met the following criteria; age $\geq$ 20 years; a proven KIT positive or activating mutation of PDGFR; prior imatinib mesylate therapy of 400 mg/day or more for at least 8 weeks; disease progression or relapse while on previous treatment with imatinib mesylate; at least one tumor lesion measurable by a computed tomographic (CT) scan or magnetic resonance imaging (MRI); an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; a life expectancy of more than 3 months; adequate organ functions as defined by: neutrophils $\geq 1.5 \times 10^3$ cells/mm^3, platelets $\geq 1.0 \times 10^4$ cells/mm^3, hemoglobin $\geq$9.0 g/dl, serum creatinine $\leq$2.0$\times$ upper limit of normal (ULN), urine protein quantitative value of $\leq$1+ on dipstick or 30 mg/dl in urinalysis, aspartate aminotransferase $\leq 2.5 \times$ ULN (5.0 $\times$ ULN in patients with liver metastasis), alanine aminotransferase $\leq 2.5 \times$ ULN (5.0 $\times$ ULN in patients with liver metastasis), alkaline phosphatase $\leq 2.5 \times$ ULN (5.0 $\times$ ULN in patients with bone or liver metastasis), and total bilirubin $\leq 2.0 \times$ ULN. This protocol was approved by the Institutional Review Board at each study site. All patients provided written informed consent.

Study design

This study was an open-label and multicenter Phase II clinical study. The primary endpoint was the objective response rate to a once daily oral treatment with 125 mg motesanib in patients with advanced GISTs who experienced disease progression or relapse while on imatinib mesylate treatment. (Sunitinib was not approved for imatinib-resistant

GIST until 2 years after their study was completed.) The secondary endpoints were duration of response, progression-free survival (PFS), time to response, overall survival, and PK profiles of motesanib in Japanese patients with advanced GISTs.

The dose was firstly reduced to 100 mg, and if need be, to 75 mg in the second time. If the grade 3 adverse event (AE) is not adequately controlled with appropriate supportive care or a grade 4 AE occurs, motesanib was withheld. Once the grade 3 or 4 AE has resolved to baseline or grade ≤ 1 for nonhematologic toxicities or baseline or grade ≤ 2 for hematologic toxicities, the dose was reduced by 25 mg and treatment was resumed. If treatment with motesanib was withheld for >21 days, the patient should be withdrawn from the treatment period and complete the end of study procedures. If a patient was receiving 75 mg and requires a dose reduction, treatment with motesanib was stopped and the patient should complete the end of study procedures.

Tumor evaluation was performed after 8 weeks and at every 8 weeks thereafter, by using the modified Response Evaluation Criteria in Solid Tumor (RECIST). A confirmation of tumor response was performed by using the modified RECIST at least 4 weeks after a complete response (CR) or PR was first documented. An appointed radiographic image reviewer who was independent of the study site or the study sponsor reviewed CT or MRI of all patients.

The severity of AEs was graded according to Common Toxicity Criteria for Adverse Events (CTCAE, version 3). Special attention was paid to cardiac function, hypertension, hypothyroidism, and cholecystitis. Laboratory assessments (serum chemistry, hematology, thyroid hormones, blood pressure, and electrocardiogram) were performed every 2 weeks.

Ten patients had the following PK parameters: maximum observed plasma concentration (C_{max}), terminal elimination half-life ($t_{1/2}$), area under the plasma concentration–time curve from time 0 to 24 h after dosing (AUC_{0-24}), concentration at 24 h after dosing (C_{24}), maximum plasma concentration time (t_{max}), the area under the plasma concentration versus time curve from 0 to infinity (AUC_{0-inf}), and apparent plasma clearance (CL/F). These PK parameters of motesanib were calculated by the standard noncompartmental model using WinNonlin software version 4.1e (Pharsight Corporation, Mountain View, CA, USA) and summarized according to the study day and history of gastrectomy using descriptive statistics. Individual plasma concentration–time profiles were summarized by history of gastrectomy.

Statistical analysis

Descriptive statistics are provided for each endpoint. The safety analysis population consisted of all patients who received at least one dose of motesanib. The objective response rate and its two-sided 95% confidence interval (95% CI) were calculated. The CI was constructed by the exact method described by Collett [10]. For a PFS, calculated as the number of days between the first dose of motesanib and the date when radiological evidence of disease progression is determined (date of CT scan/MRI), or death (regardless of cause), whichever comes first (date of PD or death minus date of first dose of motesanib), Kaplan–Meier curve (with two-sided 95% CI) was generated and its standard error was calculated using Greenwood's formula. Statistical analyses were performed using the SAS statistical software package (SAS Institute Inc., Cary, NC, USA) [11].

Results

Patient population

A total of 35 patients were enrolled and treated with motesanib between November 2005 and June 2006 at the following sites: Aichi Cancer Center Hospital, Osaka University Hospital, National Cancer Center Hospital, Hokkaido University Hospital, Niigata University Hospital, National Cancer Center Hospital East, National Hospital Organization Kure Medical Center, and Kumamoto University Hospital. One patient did not undergo baseline CT assessment. Hence, 34 patients were eligible for tumor response evaluation, and 35 for toxicity evaluation. Baseline demographic and clinical characteristics are summarized in Table 1. Of the 35 patients enrolled, 17 (49%) were female and the median age was 62.0 years (range 31–83 years). Every patient was diagnosed as having GIST with positive immunoreactivity for KIT protein. The most common primary sites of the tumor were the small intestine ($n = 17$) and the stomach ($n = 10$). The other sites of the tumor were the colon ($n = 2$) and the rectum ($n = 2$). All patients had received treatment with imatinib mesylate but not with other tyrosine kinase inhibitors. The mean time from the last imatinib treatment was 0.9 months (range 0.2–5.5 months).

Outcome measures

The tumor response as assessed by an independent radiographic image reviewer is shown in Table 2. No CR was observed among the 35 patients enrolled in this study. One patient (3%; 95% CI 0.1–14.9%) had a PR and seven patients (20%) demonstrated SD for at least 24 months, two of whom continued to have SD for more than 2 years. Twelve additional patients had SD lasting for 12 weeks or more. Thirteen patients experienced disease progression within 12 weeks. The patient with PR had a gastric GIST

Table 1 Baseline characteristics

	All patients ($N = 35$)
Sex, *n* (%)	
Female	17 (49)
Male	18 (51)
Age	
Median	62.0
Min, max	31, 83
Age group, *n* (%)	
<65 years	23 (66)
≥65 years	12 (34)
≥75 years	4 (11)
ECOG PS, *n* (%)	
0	24 (69)
1	9 (26)
2	2 (6)
Site of primary tumor at diagnosis, *n* (%)	
Small intestine	17 (49)
Stomach	10 (29)
Colon	2 (6)
Rectum	2 (6)

Table 2 Best tumor response per modified RECIST per independent review

	All patients ($N = 35$)
Patients with measurable disease at baseline	34 (97)
Response assessment, *n* (%)	
Confirmed CR	0 (0)
Confirmed PR	1 (3)
SD[a]	19 (54)
PD	13 (37)
Unevaluable[b]	1 (3)
Not done	1 (3)
Confirmed objective response (CR or PR)	1 (3)
95% CI[c]	0.1–14.9
Durable SD[d]	7 (20)

Full analysis set includes all patients who received at least one dose of motesanib

[a] Patients with a response assessment of PR or CR that is not subsequently confirmed at least 4 weeks later are included as SD

[b] Unevaluable includes patients with a response assessment of CR, PR, or SD prior to the scheduled first assessment of response without an additional assessment of response

[c] Binomial proportion with exact 95% CI

[d] Durable SD is defined as having a best response on study as SD with a duration of ≥24 weeks from study day 1

with spindle-cell type, exon 11 mutation, liver, and peritoneal metastases, and had initially responded to imatinib with SD as assessed by RECIST (Fig. 1). The median PFS

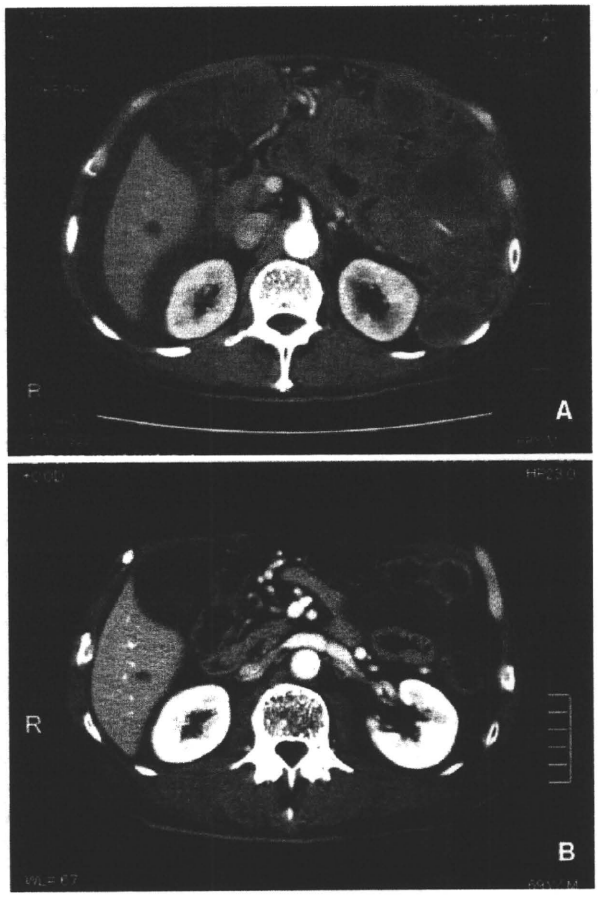

Fig. 1 A 68-year-old male with a primary GIST of the stomach and recurrent liver and peritoneal metastases. **a** Pre-treatment CT scan shows multiple low-density masses. **b** CT scan obtained after 3 months of treatment with once daily motesanib 125 mg shows that the multiple lesions have become significantly smaller and less dense

time of motesanib was 16.1 weeks (95% CI 8.4–32.0 weeks; Fig. 2).

Safety and tolerability

Table 3 summarizes treatment-related adverse events (TRAEs) (patient incidence ≥15%). The most frequent nonhematologic TRAEs included hypertension (63% of patients), diarrhea (51%), and fatigue (43%). Five patients (14%) experienced grade 3 hypertension and two patients (6%) experienced grade 3 fatigue. The only hematological toxicity was anemia (grade 2 in 3% of patients, grade 3 in 6% of patients, and grade 4 in 0% of patients). One patient (3%) experienced grade 4 hyperuricemia. No grade 5 TRAEs occurred.

Previous motesanib studies have reported an increased occurrence of cholecystitis in patients receiving motesanib,

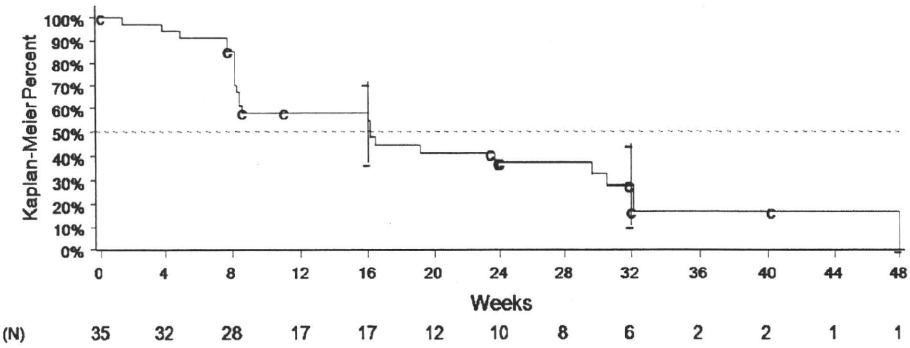

Fig. 2 Kaplan–Meier estimates of PFS

specifically at a dose of 75 mg twice daily continuously. The etiology of cholecystitis observed in patients receiving motesanib is unknown. Cholecystitis was not reported in this study. Gallbladder disorder was reported in three patients, specifically extended gallbladder or wall thickening, which was incidentally discovered in these patients on ultrasound sonography (US). The patients had not undergone US before starting motesanib treatment, nor were these disorders detected on routine CT scanning.

Figure 3 and Table 4 summarize the results of the intensive PK analyses. After a single-dose oral administration of 125 mg on day 1, motesanib was rapidly absorbed, with an overall median t_{max} of 0.75 h; a similar median t_{max} value (0.79 h) was observed after daily administration of motesanib on day 29. The mean C_{max}, AUC_{0-24}, and C_{24} were slightly lower on day 29 than on day 1, indicating that there was no accumulation after daily administration. The day 29 to day 1 mean ratios were 0.62, 0.71, and 0.80 for C_{max}, AUC_{0-24}, and C_{24}, respectively, for all evaluable patients.

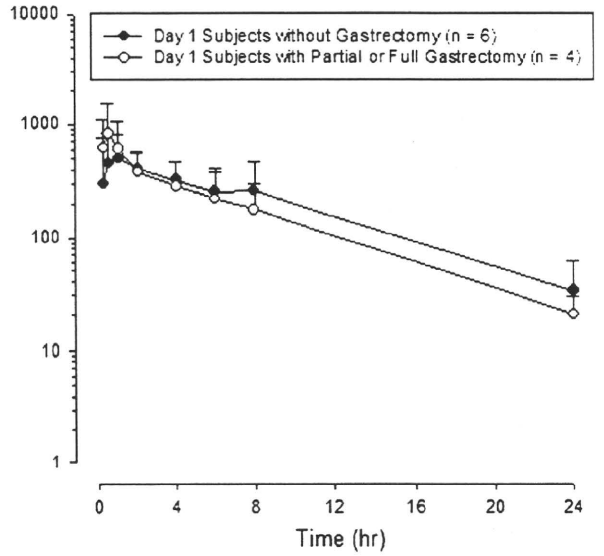

Fig. 3 Mean concentration–time profiles after oral administration of 125 mg of motesanib on day 1 in patients without gastrectomy and in patients with partial or full gastrectomy

Table 3 TRAE (15% or more of the patients)

Preferred term	Number of patients reporting TRAE, *n* (%), 35 (100)			All patients (*N* = 35)
	Grade 1/2	Grade 3	Grade 4	All grades
Anemia	1 (3)	2 (6)	0 (0)	3 (9)
Hypertension	17 (48)	5 (14)	0 (0)	22 (63)
Diarrhea	18 (51)	0 (0)	0 (0)	18 (51)
Fatigue	13 (38)	2 (6)	0 (0)	15 (43)
Headache	11 (31)	0 (0)	0 (0)	11 (31)
Weight decreased	11 (31)	0 (0)	0 (0)	11 (31)
Rash	10 (29)	0 (0)	0 (0)	10 (29)
Anorexia	5 (14)	4 (11)	0 (0)	9 (26)
Nausea	8 (23)	1 (3)	0 (0)	9 (26)
Blood thyroid-stimulating hormone increased	8 (23)	0 (0)	0 (0)	8 (23)
Dysphonia	8 (23)	0 (0)	0 (0)	8 (23)
Protein urine present	6 (17)	1 (3)	0 (0)	7 (20)
Dry skin	6 (17)	0 (0)	0 (0)	6 (17)
Vomiting	5 (15)	1 (3)	0 (0)	6 (17)

Table 4 Summary of PK parameters following oral administration of 125 mg motesanib on days 1 and 29

PK parameter	*N*	Day 1 Mean ± SD	Day 29 Mean ± SD	Day 29:Day 1 ratio Mean ± SD
All evaluable patients				
t_{max} (h)[a]	10	0.75 (0.25–2.0)	0.79 (0.50–4.0)	NA
C_{max} (ng/ml)	10	800 ± 439	488 ± 363	0.62 ± 0.20
AUC_{0-24} (μg h/ml)	9	3.87 ± 2.28	2.51 ± 2.10	0.71 ± 0.32
AUC_{0-inf} (μg h/ml)	9	4.14 ± 2.47	NA	NA
$t_{1/2,z}$ (h)	8	5.42 ± 1.51	4.27 ± 1.26	NA
CL/F (l/h)	9	41.1 ± 22.3	69.3 ± 31.8	NA
C_{24} (ng/ml)	9	27.6 ± 23.8	12.9 ± 15.4	0.80[b] ± 1.17
Evaluable patients with no prior gastrectomy				
t_{max} (h)[a]	6	1.0 (0.25–2.0)	1.0 (0.50–4.0)	NA
C_{max} (ng/ml)	6	692 ± 312	354 ± 193	0.53 ± 0.16
AUC_{0-24} (μg h/ml)	5	3.91 ± 2.43	1.93 ± 0.67	0.67 ± 0.39
AUC_{0-inf} (μg h/ml)	5	4.27 ± 2.73	NA	NA
$t_{1/2,z}$ (h)	4	5.20 ± 1.79	4.32 ± 1.89	NA
CL/F (l/h)	5	40.7 ± 24.5	71.5 ± 26.0	NA
C_{24} (ng/ml)	5	33.5 ± 31.1	16.6 ± 20.3	1.11[b] ± 1.57
Evaluable patients with partial or full gastrectomy				
t_{max} (h)[a]	4	0.50 (0.25–2.0)	0.50 (0.50–1.0)	NA
C_{max} (ng/ml)	4	962 ± 599	689 ± 492	0.75 ± 0.21
AUC_{0-24} (μg h/ml)	4	3.82 ± 2.45	3.23 ± 3.16	0.75 ± 0.25
AUC_{0-inf} (μg h/ml)	4	3.99 ± 2.49	NA	NA
$t_{1/2,z}$ (h)	4	5.63 ± 1.42	4.22 ± 0.38	NA
CL/F (l/h)	4	41.6 ± 22.9	66.4 ± 42.2	NA
C_{24} (ng/ml)	4	20.2 ± 9.2	8.37 ± 6.24	0.40 ± 0.16

Note: One patient did not have intensive sampling for day 29. This patient was excluded from the summary statistics

Parameters are presented to three significant figures when possible. Ratios are presented to two decimal places

Patients with elevated motesanib concentrations at 24 h post-dose were excluded from the C_{24}, $t_{1/2}$, AUC, and AUC-derived parameter summary statistics calculations, hence the reduced sample size for these parameters

t_{max} = the time the maximal plasma concentration was observed; C_{max} = the maximal observed plasma concentration after dosing; AUC_{0-24} = the area under the plasma concentration–time curve from time 0 to 24 h post-dose; AUC_{0-inf} = the area under the plasma concentration–time curve from time 0 to infinite time; $t_{1/2,z}$ = estimated terminal-phase half-life; CL/F = apparent clearance (AUC_{0-24} was used to estimate CL/F on day 29); C_{24} = the observed plasma concentration at 24 h after dosing; *NA* not applicable

[a] t_{max} is reported as a median (range) value, and is presented to two significant figures

[b] One patient had a C_{24} ratio of 3.84. The C_{24} ratio (mean ± SD) excluding this patient is 0.42 ± 0.30 for all patients and 0.43 ± 0.42 for patients without gastrectomy

For the patients who had partial or full gastrectomy ($n = 4$), day 1 C_{max} values were slightly higher (<2-fold) and AUC values were similar to those who had no gastrectomy. Means for C_{max} and AUC values on day 29 were higher compared with those who had no gastrectomy but not significant. Median t_{max} values occurred earlier in patients with gastrectomy on both days 1 and 29 (median t_{max} = 0.50 h with gastrectomy versus 1.0 h with no gastrectomy). C_{24} values on days 1 and 29 were lower in patients with gastrectomy compared with those who had no gastrectomy, though the mean $t_{1/2}$ values were similar (mean $t_{1/2,z}$ value = 4.22 versus 4.32 h, respectively).

Discussion

Although regression of thyroid cancer, renal cell carcinoma, and leiomyosarcoma was observed in the Phase I study of motesanib [12], objective tumor regression was observed in only one patient (3%) with GIST in this study. Motesanib administered as a single-agent was well tolerated, and a number of patients experienced prolonged stabilization of the disease. Seven (20%) did not exhibit disease progression for a minimum of 24 weeks, and the median PFS was 16.1 weeks. Serious hematological AEs (grade 3/4) were observed after sunitinib treatment in the Phase III trial. The incidence of grade

3/4 anemia, leukocytopenia, and neutrocytopenia was 4, 4, and 10%, respectively [9]. Anemia, leukocytopenia, and neutropenia were also reported as AEs for patients treated with imatinib; the incidence of grade 3/4 anemia, leukocytopenia, and neutropenia in a large Phase III study was 2.0, 1.4, and 4.8%, respectively [6]. The only hematological toxicity of motesanib was anemia (grade 2, 3%; grade 3, 6%). Despite long-term exposure to motesanib, hematological toxicities were mild. Motesanib may therefore present an alternative treatment option for patients who experienced neutrocytopenia or thrombocytopenia after treatment with imatinib or sunitinib.

To evaluate the potential effect of gastrectomy on motesanib disposition, the motesanib PK profiles from patients with a history of gastrectomy were compared with those who did not have prior gastrectomy. Median t_{max} values occurred earlier in patients with gastrectomy on both days 1 and 29, suggesting faster absorption in patients with a history of gastrectomy. Since gastrectomy impacts the gastric emptying rate and the absorption rate resulting in increase in C_{max}, these findings should be considered in the following clinical trials.

The current treatment options for patients with GIST after treatment failure with imatinib and sunitinib are limited to best supportive care and investigative therapies. This study shows that in Japanese patients with advanced GIST motesanib is well tolerated, and, although an objective tumor response was observed in only one patient, motesanib may have an impact on survival in a retrospective analysis. However, focusing on other clinically meaningful measures, such as the Choi criteria [13] that incorporating tumor density and small changes in tumor size as revealed by CT scanning, is more important than focusing on the tumor response rate, which may fail to identify a potentially effective therapy [14, 15]. Randomized, well-controlled studies with time to progression or survival as the primary endpoints of efficacy will be needed to identify agents for which a tumor regression effect is not anticipated. Results from such studies will help in making an informed decision of whether or not to continue the clinical development of such agents in GIST.

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Phase I and Pharmacokinetic Study of ABI-007, Albumin-bound Paclitaxel, Administered Every 3 Weeks in Japanese Patients with Solid Tumors

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Objective: ABI-007 is a novel Cremophor® EL-free nanoparticle albumin-bound paclitaxel. This Phase I study was designed to evaluate tolerability and determine recommended dose for Japanese patients when ABI-007 was administered in every-3-week schedule. Pharmacokinetics of paclitaxel was also assessed.

Methods: Patients with advanced solid tumors refractory to standard therapy received a 30 min intravenous infusion of ABI-007 every 3 weeks without pre-medications at 200, 260 or 300 mg/m^2, respectively. Tolerability and recommended dose were determined by the standard '3 + 3' rule.

Results: No dose-limiting toxicity was observed, despite the dose escalation. In another cohort, 260 mg/m^2 was re-evaluated and resulted in no dose-limiting toxicity. Grade 3 or 4 neutropenia was reported for the majority of patients ($n = 8$) but no incidence of febrile neutropenia. Non-hematological toxicities were generally mild except for Grade 3 sensory neuropathy ($n = 3$). Pharmacokinetic study demonstrated the area under the curve of paclitaxel increased with increasing the dosage, and comparable pharmacokinetic parameters to the western population. Partial response was observed in three non-small cell lung cancer patients. Two of whom had received docetaxel-containing chemotherapy prior to the study.

Conclusions: ABI-007 administered in every-3-week schedule was well tolerated up to 300 mg/m^2, and recommended dose was determined at 260 mg/m^2 in consideration of efficacy, toxicities and similarity of pharmacokinetic profile in western studies. Additional studies of single-agent ABI-007 as well as platinum-based combinations, particularly in patients with non-small cell lung cancer, are warranted.

Key words: nanoparticle albumin-bound paclitaxel – ABI-007 – Phase I – pharmacokinetic – Japanese

INTRODUCTION

ABI-007 (Abraxane®; Abraxis Bioscience, Los Angels, CA, USA) is a novel Cremophor® EL (polyoxyethylated castor oil)-free albumin-bound nanoparticle formulation of paclitaxel. This formulation allows for a higher paclitaxel concentration in the suspension, serving to reduce the administration volume and time. No pre-medication to prevent the Cremophor® EL-induced hypersensitivity reaction is needed. In addition, non-polyvinyl chloride infusion system and in-line filtration are not necessarily applied given no leaching of plasticizers (1,2).

In the Phase I study of every-3-week (Q3W) schedule conducted in the USA, the dose of ABI-007 was escalated from 135 to 375 mg/m^2, and maximum tolerated dose (MTD) and recommended dose (RD) were established at 300 mg/m^2. It was exceedingly higher than that of solvent-based paclitaxel (Taxol®; Bristol–Myers Squibb, Princeton, NJ, USA), 175 mg/m^2 (1). Dose-limiting toxicities (DLTs) were keratitis, blurred vision, sensory neuropathy, stomatitis and neutropenia. Maximum concentration (C_{max}) and the area under the curve from time zero to infinity (AUC_{inf}) of paclitaxel increased linearly over the ABI-007 dose range of 135–300 mg/m^2 administered over 30 min. Volume of distribution of ABI-007 is characterized by the larger distribution than solvent-based paclitaxel, indicating extensive extravascular distribution of the drug (3). C_{max} and AUC_{inf} values for individual patients correlated well with toxicities.

In the Phase III pivotal study of 454 patients with metastatic breast cancer, Q3W schedule of ABI-007 260 mg/m^2 produced the superior outcome to the same schedule of solvent-based paclitaxel, 175 mg/m^2: significantly higher response rate and prolonged time to progression [33% vs. 19% ($P < 0.001$) and 23.0 vs. 16.9 weeks ($P = 0.006$), respectively] and significantly lower incidence of Grade 4 neutropenia, despite a 49% higher paclitaxel dose [9% vs. 22% ($P < 0.001$)] (4). The dosage and schedule used in this Phase III study lead to the approved labeling worldwide.

According to the clinical utility and study data reported overseas, ABI-007 seems to be an effective treatment. This Phase I study aimed to evaluate tolerability, DLT and RD in Japanese patients with solid tumors when administered in Q3W schedule. Efficacy, toxicity and pharmacokinetics (PK) were also evaluated as secondary objectives, followed by the evaluation on ethnic difference in PK.

PATIENTS AND METHODS

Patient Eligibility

Patients aged 20–74 years with histologically or cytologically diagnosed malignant solid tumors refractory to standard therapies or for which there was no effective treatment were eligible. They had to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and a life expectancy of ≥60 days. Eligibility criteria also included adequate renal, liver and bone marrow function, defined as serum creatinine (Cr) ≤1.5 mg/dl, serum total bilirubin (TB) ≤1.5 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <100 IU/l, respectively, serum albumin ≥3.0 g/dl, white blood cell count ≤12 000/mm^3, absolute neutrophil count ≥2000/mm^3, platelets ≥100 000/mm^3 and hemoglobin ≥9.0 g/dl. Patients with prior exposure to taxanes were eligible for the study. Key exclusion criteria included the following: (i) surgery within 4 weeks; (ii) chemotherapy within 3 weeks; (iii) radiotherapy within 3 weeks; (iv) history of radiation to more than 30% of hematopoietic marrow; (v) pre-existing sensory neuropathy ≥Grade 2; (vi) pleural effusion and ascites that required drainage; (vii) brain metastasis showing symptoms or requiring treatment; (viii) hepatitis B or C virus or human immunodeficiency virus infection; (ix) chronic steroid treatment; (x) pregnancy, lactation, suspicion of being pregnant; (xi) serious pre-existing medical conditions such as uncontrolled infections, pulmonary fibrosis, diabetes, severe heart disease and psychogenic disorders.

This study was approved by the Institutional Review Board at the National Cancer Center and conducted according to Japanese Good Clinical Practice guidelines. All patients provided written informed consent prior to study entry.

Study Design and Treatment

This Phase I, open label, dose-finding study was conducted at National Cancer Center and National Cancer Center East.

ABI-007 was supplied by TAIHO Pharmaceutical Co., Ltd, Tokyo Japan. Each vial contained 100 mg of paclitaxel and ~900 mg of frozen-dried Albumin Human (United States Pharmacopeia). The prescribed dose of ABI-007 was prepared in 5 mg (paclitaxel)/ml of physiological saline as a suspension. The drug was administered via 30 min i.v. without pre-medication and in-line filtration.

Evaluated dose levels were 200, 260 or 300 mg/m^2, as shown in Table 1, repeated every 3 weeks. The rationale for selected dose range was the following: the upper level, 300 mg/m^2—MTD determined in a US Phase I study; the middle level, 260 mg/m^2—the approved dose in the US/EU, and the lower level, 200 mg/m^2—one dose level below MTD examined in the foregoing Phase I study. The dose range also factored in PK: linear PK of ABI-007 over the dose range 80–300 mg/m^2 and the same level and activity of CYP2C8 and CYP3A4 between Japanese and Caucasians (5). Dose escalation was capped at 300 mg/m^2. In the event that MTD exceeded the cap, further steps in investigation would be discussed among study sponsor, principal investigator and medical experts.

The dose escalation followed the standard '3 + 3' rule. Three patients were evaluated at the first dose level, and in the absence of DLTs, three additional patients were entered at the next dose level. If one of the three patients encountered a DLT, another cohort was to be added at the same dose level. The MTD was defined as the dose level at which two out of three to six patients experienced DLT. The RD

Table 1. Dose levels

Level	Dose (mg/m^2)	No. of patients entered	No. of courses
1	200	3	9
2	260	6	23
3	300	3	14

was defined as the dose level that is one level below MTD, and consequently, a total of six patients were to be treated at RD to further evaluate the safety profile.

DLTs were pre-defined as any of the following drug-related toxicities that had occurred during the first course: (i) Grade 4 thrombocytopenia; (ii) Grade 3 thrombocytopenia requiring platelet transfusion; (iii) Grade 4 neutropenia over 4 days; (iv) Grade 3 or 4 febrile neutropenia; and (v) Grade 3 or 4 non-hematologic toxicity. Dose was reduced by one level when DLT occurred in the first course, and reduction was allowed when the toxicities corresponding to DLT or Grade 2 neuropathy occurred in the second course or later.

Patient Evaluation

Pre-treatment evaluation included a complete history and physical examination, a complete blood count with differential, serum chemistry profile, urinalysis including pregnancy test, chest X-ray and electrocardiogram. Serum chemistry profile included electrolytes, Cr, urea nitrogen, TB, AST, ALT, lactic dehydrogenase, alkaline phosphatase, total protein, albumin and C-reactive protein. Baseline imaging studies and serum tumor marker levels were obtained at the discretion of treating physician. Toxicity assessment, physical examination and all blood tests except serum tumor markers were repeated on a weekly basis.

Toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Patients were considered evaluable for toxicity if they received at least one dose of the study drug. Objective response to therapy was assessed every 4–6 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 (6).

Blood Sampling and PK Analysis

Whole blood samples of 7 ml each were collected in 6 ml of heparinized tube and 1 ml of K3-EDTA tube to determine the PK of ABI-007 at time points: 0, 0.25, 0.5 (end of infusion), 0.75, 1, 1.5, 2, 4, 10, 24, 48 and 72 h. Heparinized samples were immediately centrifuged at 1000 *g* for 15 min in 4°C and resultant plasma was stored in aliquot, whereas K3-EDTA samples were softly mixed in normal temperature. These samples were stored at less than or equal to −20°C until analyzed. The sample was analyzed for paclitaxel using liquid chromatography/tandem mass spectrometry in Alta Analytical Laboratory (El Dorado Hills, CA, USA). The limit of quantification for paclitaxel in plasma and whole blood was 1.00 and 5.00 ng/ml, respectively, and the range of reliable response in these samples was 1.00–500 and 5.00–5000 ng/ml, respectively.

PK parameters were determined from each patient's whole blood/plasma paclitaxel concentration profile. They were evaluated by non-compartmental analysis using the WinNonlin software package (Ver4.1, Pharsight Corp., CA, USA). The C_{max} of paclitaxel was obtained directly from experimental data. The elimination constant (λz) was obtained by log-linear regression analysis of the terminal phase of the whole blood/plasma concentration vs. time profile. The elimination half-life ($t_{1/2}$) was determined by taking the ratio of natural log of 2 and λz. The AUC_{inf} was estimated by summing the areas from time zero to the last measured concentration–time point (AUC_{0-t}), calculated using the linear-logarithmic trapezoidal method, and the extrapolated area. The dose–area relationship (i.e. total ABI-007 dose divided by AUC_{inf}) was used to determine total body clearance (CL). The volume of distribution (Vz) was determined by taking the ratio between CL and λz.

Table 2. Patient characteristics

Characteristics	No. of patients
Total no. of patients	12
Male/female	10/2
Age (years)	
Median	61
Range	45–69
ECOG performance status	
0	3
1	9
Tumor type	
NSCLC	6
Parotid gland	1
Ovary	1
Bladder	1
Pharyngeal and esophageal	1
Colon	1
Thymoma	1
Prior treatment	
Surgery	9
Radiotherapy	3
Chemotherapy	12
No. of prior chemotherapy	
1	1
2	4
≥3	7
Prior taxane therapy	
Yes	
Solvent-based paclitaxel	1
Docetaxel	5
Solvent-based paclitaxel and docetaxel	2
No	4

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

Table 3. Hematologic toxicities (all courses)

Dose levels	Level 1 (200 mg/m^2)			Level 2 (260 mg/m^2)			Level 3 (300 mg/m^2)			All		
No. of patients (no. of courses)	$n = 3$ (9)			$n = 6$ (23)			$n = 3$ (14)			$n = 12$ (46)		
CTCAE grade	1–2	3	4	1–2	3	4	1–2	3	4	1–2	3	4
Leucopenia	2	0	0	3	2	0	3	0	0	8	2	0
Neutropenia	1	1	0	1	3	1	1	2	0	2	6	2
Anemia	1	0	0	2	0	0	1	0	0	4	0	0
Thrombocytopenia	0	0	0	1	0	0	1	0	0	2	0	0

CTCAE, Common Terminology Criteria for Adverse Events.

Descriptive statistics were used for baseline characteristics, safety assessment, and PK variables. Regression analysis of individual C_{max}, and AUC_{inf} vs. dose was performed to gain an appreciation of PK linearity. The SAS software package (ver8.2, SAS Institute, Inc., NC, USA) was used for statistical analysis.

RESULTS

Patients and Treatment

Between August 2006 and June 2007, 12 patients were enrolled and treated in this study at two participating centers in Japan. Patient characteristics are summarized in Table 2. Most patients were male (83%) with a median age of 61 (range, 45–69) years and all patients were ECOG PS 0–1. The predominant type of tumor was non-small cell lung cancer (NSCLC). Nine patients had surgery for primary tumors, seven had received more than three prior chemotherapy regimens and eight had received prior taxane-containing chemotherapy.

The patients were treated at the following dose levels: 200 mg/m^2 (Level 1, $n = 3$), 260 mg/m^2 (Level 2, $n = 6$) and 300 mg/m^2 (Level 3, $n = 3$). All were evaluable for safety and PK, and 11 for efficacy (one had no adequate measurable lesions for RECIST criteria).

DLT, Tolerability and RD

No DLTs were observed through the dose escalation to the highest Level 3; therefore, the MTD was not reached methodologically. To decide on the potential RD, study sponsor, medical advisor and principal investigators jointly reviewed the reference data in the foreign studies (1,4,7) and favored 260 mg/m^2 from tolerability and safety perspectives, particularly the development of cumulative neurotoxicity. Additional three patients were then accrued to 260 mg/m^2 cohort to repeat the assessment. None of DLTs being experienced by the additional patients, 260 mg mg/m^2, was established as RD.

Safety

A total of 46 courses of ABI-007 was administered, and the median number of courses administered per patient was 3 (range, 1–11). No acute hypersensitivity reactions were observed during the infusion period. The most common toxicities were neutropenia, leucopenia, lymphopenia, alopecia and sensory neuropathy. The incidences of hematologic toxicities by dose level are shown in Table 3. Grade 3 or 4 neutropenia was often experienced in more than half of patients throughout the study; however, no febrile neutropenia was observed. The median time to onset of Grade 3 or 4 neutropenia was 15.0 (range, 8–34) days, and the median time to recovery to <Grade 2 was 6.5 (range, 3–14) days. There were no episodes of ≥Grade 2 or greater thrombocytopenia, and anemia was mostly mild. Frequent non-hematological toxicities were sensory neuropathy, alopecia, arthralgia/myalgia and rash (Table 4). The sensory neuropathy was manifested by paresthesia in a symmetric, stocking/glove distribution, and the median time to the first indication or exacerbation from the baseline was 7 days. The severity of non-hematologic toxicities was generally mild except for three cases of Grade 3 sensory neuropathy at Level 2 ($n = 1$) and Level 3 ($n = 2$), which cumulatively exacerbated from Grade 1 observed in the first week of the first course (range, 3–6 days from the administration) to Grade 3 during the third or later course (range, 3–11 courses from the administration). Among the three patients who experienced Grade 3 sensory neuropathy, one patient had received taxane-containing chemotherapy prior to the study. A variety of ocular toxicities including superficial keratopathy reported in the initial Phase I study of USA were not observed in this study. Treatment delay occurred in one patient at each Levels 2 and 3 due to the neurotoxicity, dose reduction occurred in two patients at each Levels 2 and 3 due to the neurotoxicity, and treatment was discontinued in three patients at each Levels 2 and 3, comprising five patients with treatment-related neurotoxicity and one patient with unrelated neutropenia.

Table 4. Non-hematologic toxicities (all courses)

Dose levels	Level 1 (200 mg/m^2)		Level 2 (260 mg/m^2)		Level 3 (300 mg/m^2)		All	
No. of patients (no. of courses)	$n = 3$ (9)		$n = 6$ (23)		$n = 3$ (14)		$n = 12$ (46)	
CTCAE grade	1–2	3	1–2	3	1–2	3	1–2	3
Sensory neuropathy	1	0	5	1	1	2	7	3
Alopecia	3	0	4	0	3	0	10	0
Myalgia	0	0	6	0	3	0	9	0
Rash	2	0	4	0	1	0	7	0
Arthralgia	1	0	4	0	2	0	7	0
Asthenia	2	0	2	0	2	0	6	0
Motor neuropathy	0	0	3	0	2	0	5	0
Nausea	2	0	1	0	1	0	4	0
Anorexia	3	0	1	0	0	0	4	0
Vomiting	1	0	2	0	0	0	3	0
Diarrhea	2	0	0	0	0	0	2	0
Stomatitis	0	0	0	0	2	0	2	0

Grade 4 toxicities were not observed.

Table 5. Anti-tumor response

	Tumor type	Prior taxane therapy	Response
Level 1 (200 mg/m^2)	NSCLC	+	PD
	NSCLC	+	PR
	Parotid gland	+	PD
Level 2 (260 mg/m^2)	NSCLC	+	PD
	NSCLC	−	PR
	Ovary	+	PD
	NSCLC	+	PR
	Colon	−	PD
	Thymoma	−	SD
Level 3 (300 mg/m^2)	Bladder	−	SD
	NSCLC	+	NE
	Pharyngeal and esophageal	+	SD

PD, progressive disease; PR, partial response; SD, stable disease; NE, not evaluable.

Response

Eleven of 12 patients were evaluable for anti-tumor response (Table 5). Partial responses were observed in three NSCLC patients. Of them, two of whom had received docetaxel-containing chemotherapy prior to the study. The first patient, entered at Level 1, had received 6 courses of ABI-007, and the second and third patients, entered at Level 2, 11 and 6 courses, respectively. The both responders in Level 2 attained disease control until the treatment discontinuation due to the sensory neuropathy.

Pharmacokinetics

Blood samples for PK analysis were available from all of 12 patients following the first course of treatment. A semi-log plot of the mean values of paclitaxel concentration for each dose level vs. time is shown in Fig. 1. After 30 min infusion of ABI-007, the concentration of paclitaxel began to decrease immediately upon cessation of the infusion with $t_{1/2}$ of 17.3–27.3 h in the whole blood, which is nearly comparable with that of standard dose of solvent-based paclitaxel (6), and the decline of paclitaxel concentration from maximum was multiphasic.

The mean PK parameters of paclitaxel are summarized in Table 6. C_{max}, AUC_{0-t} and AUC_{inf} of paclitaxel when administered as a 30 min infusion of ABI-007 increased with increasing dosage. CL and Vz of the blood sample showed the small inter-patient variability, and the mean ± SD values (CV%) for CL and Vz at the dose level of 260 mg/m^2 were 18.1 ± 2.33 (12.9 CV%) (l/h/m^2) and 510 ± 96.8 (19.0 CV%) (l/m^2), respectively. These values slightly decreased with increased dosage. It was considered that there was no remarkable difference in calculated values of PK parameters between whole blood and plasma. Regression analysis suggested the dose-proportionality of ABI-007 within the dose range in this study (R^2 of $C_{max} = 0.4470$, R^2 of

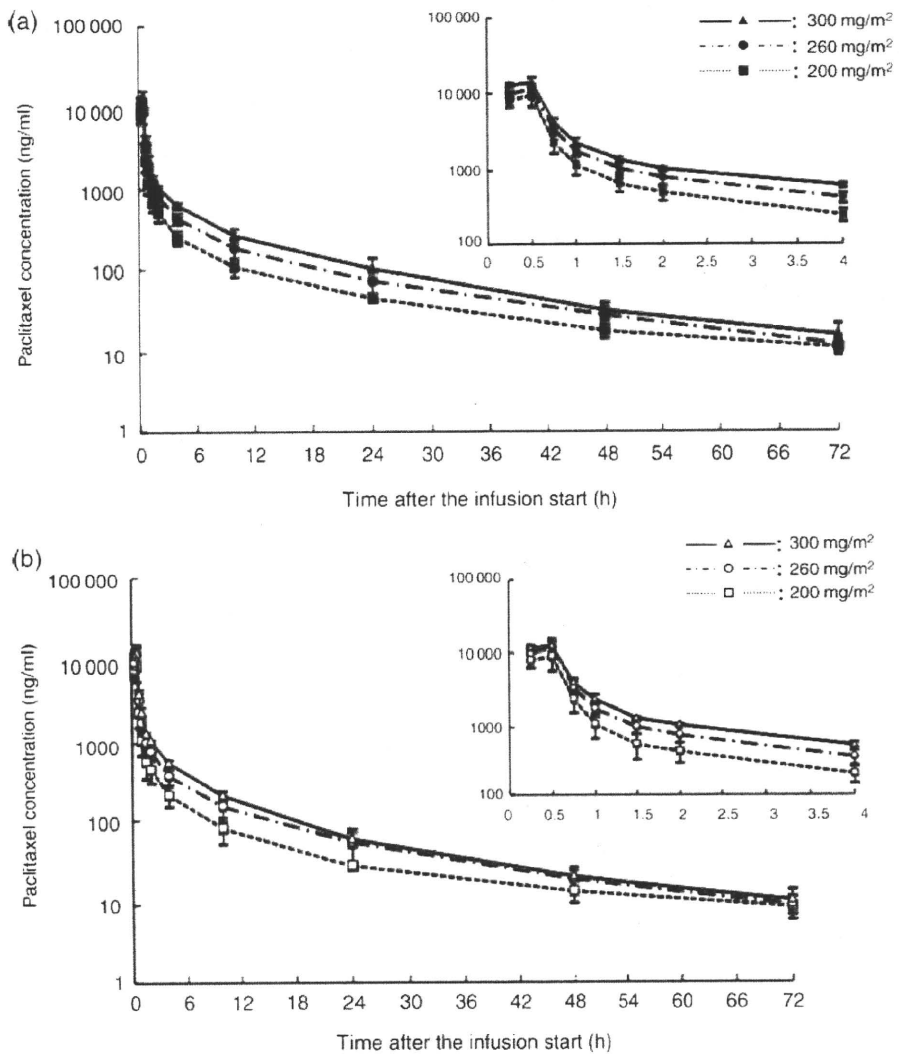

Figure 1. (a) Mean whole blood concentration–time profiles of paclitaxel. (b) Mean plasma concentration–time profiles of paclitaxel.

$AUC_{inf} = 0.7177$); however, it was difficult to establish the linearity due to those narrow dose range and small data size.

DISCUSSION

In the Phase I study where ABI-007 was administered in Q3W schedule in Japanese patients, no DLT occurred at any dose level of 200, 260 and 300 mg/m^2. Because MTD was not reached by the 3 + 3 rule, selection of RD was attributed to the consideration of reasonable tolerability, toxicities and PK profile. Since paclitaxel treatment was characterized for the cumulative neurotoxicity, dose selection also took into account the development of sensory neuropathy throughout the study. Consequently, 260 mg/m^2 was reassessed as potential RD and established as RD in the absence of applicable DLT. Outcome of sensory neuropathy in all treatment courses also provided the justification for the feasibility of 260 mg/m^2 (Table 7). Among 260 and 300 mg/m^2 cohorts, every patient experienced neuropathic events, in which Grade 3 or 4 event was more frequent in 300 mg/m^2 (two out of three patients) than in 260 mg/m^2 cohorts (one out of six patients). Moreover, all the three patients in 300 mg/m^2 cohort discontinued the treatment due to neuropathic events as opposed to two out of six patients in 260 mg/m^2 cohort.

In terms of treatment-related toxicities, Grade 3 or 4 neutropenia was experienced in 15 of 46 treatment courses (32%). Nonetheless, no febrile neutropenia was observed. Median duration of recovery from Grade 3 or 4 to <Grade 2 was 6.5 days (range, 3–14). No treatment delay was caused by neutropenia. In addition, platelet decrease ≥Grade 2 was not observed throughout the study. On the whole, hematological toxicities were mild. In regard to sensory neuropathy, the median time to the first indication or exacerbation from the baseline was 7 days, which

was relatively early to that of solvent-based paclitaxel. Especially for Grade 3 sensory neuropathy, the indication or exacerbation fell within the first week of the first course, ranging from 3 to 6 days; the time to improve from Grade 3 to Grade 2 or 1 was 21, 26 and 46 days in the respective cases. Although the improvement tended to delay when compared with median 22 days in a previous Phase III study (4), it still remains controversial because of the great difference in the sample sizes between the two studies. Meanwhile, other non-hematological toxicities including mucositis—the DLT of the US Phase I study—were generally mild to moderate up to 300 mg/m^2.

PK profiles of ABI-007 have revealed the small inter-patient variability, and the AUC and C_{max} of paclitaxel increased with increasing the dosage. In whole blood samples, there was a significant correlation between the doses and PK parameters. The linearity was uncertain in the face of wide confidence interval (CI) with small sample size, however, presumable from the other reported data showing the linearity over a wide dose range: 80–300 mg/m^2 (2) and PK equality between Japanese and western population (3).

Anti-tumor response was demonstrated in the patients with NSCLC including the patients who had received prior taxane-containing therapy.

Multiple previous studies of ABI-007 also reported the promising data in the patients with NSCLC. In a Phase II trial, 260 mg/m^2 of ABI-007 was administered alone in the same Q3W schedule as our study in the first-line setting, overall response rate was 16.3% (95% CI, 5.24–27.31%) and the disease control rate was 48.8% (95% CI, 33.90–63.78%) (8). More recently, weekly (QW) schedule of ABI-007 was also reported: 125 mg/m^2 of ABI-007 was administered in monotherapy on days 1, 8 and 15 every 4 weeks, the response rate was 30% ((95% CI, 16–44%) and the disease control rate was 50% (95% CI, 35–66%) (9). Despite the higher incidence of ≥Grade 3 neutropenia and sensory neuropathy relative to the Q3W schedule, QW schedule was well tolerated and active.

In conclusion, no DLT observed at any dose levels, and ABI-007 was well tolerated up to 300 mg/m^2 in Japanese

Table 6. PK parameters of paclitaxel

	200 mg/m^2 (n = 3)		260 mg/m^2 (n = 6)		300 mg/m^2 (n = 3)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
Whole blood						
C_{max} (ng/ml)	9430	28.3	11 635	13.0	13 833	15.3
AUC_{inf} (ng h/ml)	10 360	22.0	14 593	13.7	19 138	12.2
$t_{1/2}$ (h)	24.3	10.9	19.5	7.9	18.3	1.9
CL (l/h/m^2)	19.9	21.6	18.1	12.9	15.8	11.2
Vz (l/m^2)	689	15.3	510	19.0	417	9.7
Plasma						
C_{max} (ng/ml)	9040	34.0	12 000	17.6	12 700	20.5
AUC_{inf} (ng h/ml)	9146	29.6	13 330	20.7	16 271	11.2
$t_{1/2}$ (h)	29.0	17.7	20.8	19.5	19.8	9.8
CL (l/h/m^2)	23.1	26.4	20.2	21.5	18.6	10.6
Vz (l/m^2)	935	11.7	620	36.9	527	7.0

PK, pharmacokinetic; CV, coefficient of variation; C_{max}, maximum concentration; AUC_{inf}, area under the concentration–time curve up to ∞ hours; $t_{1/2}$, terminal elimination half-life; CL, clearance; Vz, volume of distribution based on terminal phase.

Table 7. Grade change in sensory neuropathy (all courses)

Level	Case	Before administration	Course no.										
			1	2	3	4	5	6	7	8	9	10	11
Level 1	1-2	0	0	0	1	1	1	1[a]	—	—	—	—	—
Level 2	2-1	1	2	—	—	—	—	—	—	—	—	—	—
	2-2	0	1	1	1	1	1	1	1	1	2	2	3[a]
	2-3	0	0	1	—	—	—	—	—	—	—	—	—
Level 3	3-1	0	1	1	2	2	2	3[a]	—	—	—	—	—
	3-2	0	1	1	1	2	2[a]	—	—	—	—	—	—
	3-3	0	2	2	3[a]	—	—	—	—	—	—	—	—
Level 2	2-4	0	1	1	1	2	2	2[a]	—	—	—	—	—
	2-5	0	1	—	—	—	—	—	—	—	—	—	—
	2-6	0	1	1	—	—	—	—	—	—	—	—	—

—, end of study.
[a]Study-off due to sensory neuropathy.

patients. RD in this schedule was determined to be 260 mg/m^2 in consideration of efficacy, toxicities and similarity of PK profile in the western studies. Additional studies of single-agent ABI-007 and platinum-based combinations are warranted.

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Conflict of interest statement

Hironobu Minami and Tomohide Tamura receive remuneration for the lectures from Taiho Pharmaceutical (Tokyo, Japan).

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ORIGINAL ARTICLE

Phase 1 study of the investigational, oral angiogenesis inhibitor motesanib in Japanese patients with advanced solid tumors

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Abstract

Purpose The aim of this study was to investigate the safety and pharmacokinetics of motesanib (AMG 706), a small-molecule antagonist of vascular endothelial growth factor receptors 1, 2, and 3, platelet-derived growth factor receptor, and c-Kit in Japanese patients with advanced solid tumors.

Methods Patients were administered motesanib orally once daily (QD) at doses of 50, 100, and 125 mg QD. The total study duration for each patient consisted of three cycles of 28 days per cycle. The primary endpoints were the incidence of dose-limiting toxicities (DLTs), estimation of the maximum tolerated dose (MTD), and assessment of pharmacokinetic parameters of motesanib.

Results Fifteen patients were enrolled and received motesanib. No DLTs were observed and, therefore, the MTD was not reached. Motesanib had acceptable toxicity at doses up to 125 mg QD. The pharmacokinetics of motesanib appears to be dose proportional. No objective responses per RECIST were observed. However, all 15 patients achieved stable disease, and five patients had durable (>24 weeks) stable disease.

Conclusions The results of this study demonstrate that motesanib is tolerable in Japanese patients at doses up to 125 mg QD.

Keywords Motesanib · Advanced solid tumors · Pharmacokinetics · Maximum tolerated dose

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Introduction

Cancer is the leading cause of death in Japan [1]. Despite the use of surgery, chemotherapy, radiation therapy, and other treatments, more than 325,000 Japanese are estimated to die of cancer each year [1] and, consequently, attention has focused on the development of novel treatments for cancer. In particular, because solid tumors are dependent on the development of vascular networks for continued growth and development, there has been interest in inhibition of angiogenesis (the process by which new blood vessels develop) as an anticancer therapy [2–4]. Antiangiogenic agents have been shown to have antitumor activity in preclinical models of human cancer [5–7] and to have clinical activity in the treatment of advanced solid tumors [8–11].

Vascular endothelial growth factor (VEGF) is among the most potent proangiogenic factors [12, 13]. The effects of VEGF on the vasculature are mediated by activation of its receptors, the receptor tyrosine kinases VEGFR1 (Flt-1) and VEGFR2 (KDR), with most of the proangiogenic effects of VEGF being mediated by VEGFR2 [12]. In addition to its effects on cellular proliferation, activation of the platelet-derived growth factor receptor (PDGFR) may also

contribute to angiogenesis by both increasing VEGF expression and promoting migration of endothelial cells [14–16].

Motesanib (AMG 706) is an orally administered small-molecule antagonist of VEGFR1, 2, 3; PDGFR, and c-Kit, and is currently in development for the treatment of solid tumors [17]. Furthermore, in a phase 1 study conducted in the US, motesanib was shown to have promising antitumor activity and acceptable toxicity [18]. The aims of this study were to investigate the safety (including the maximum tolerated dose [MTD]), pharmacokinetics, antitumor activity, and pharmacodynamics of motesanib in Japanese patients with advanced solid tumors.

Patients and methods

Patients

Eligible patients were aged 20–74 and had histologically or cytologically documented advanced solid tumors that were refractory to standard therapy or for which no standard therapy was available. Additional inclusion criteria were an Eastern Cooperative Oncology Group performance status of $\leq$2, absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin $\geq$9.5 g/dl, serum creatinine $\leq$1.5 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$80 IU/l, alkaline phosphatase $\leq$1,000 IU/l, and total bilirubin $\leq$1.8 mg/dl. Patients were excluded from the study if they had hematologic malignancy; central nervous system metastases requiring therapy or with symptoms; non-small-cell lung cancer with squamous cell histology in the hilar regions; active multiple primary cancer; history of bleeding, diathesis, or hypercoagulopathy; history of arterial thrombosis; history of cardiovascular disease including myocardial infarction, congestive heart failure, uncontrolled hypertension (diastolic >85 mm Hg, systolic >145 mm Hg), and arrhythmia; concurrent interstitial pneumonitis, pulmonary fibrosis, hemoptysis, diabetes or poorly controlled diabetes; or pleural effusion or ascites requiring drainage. Patients were also excluded if they had received previous treatment with small-molecule VEGF receptor inhibitors; received chemotherapy, radiation therapy, or surgery within 4 weeks of study day 1; received antibody treatment within 12 weeks of study day 1; or received anticoagulation therapy within 7 days of study day 1. This protocol was approved by the Institutional Review Board of National Cancer Center (Tokyo, Japan). All patients provided written informed consent.

Study design

This was a phase 1, single-center, open-label, sequential dose-escalation study conducted in Japan. The primary endpoints were the incidence of dose-limiting toxicities (DLTs; defined later), estimation of the MTD, and assessment of pharmacokinetic parameters of motesanib following oral administration. Secondary endpoints included the incidence of adverse events, changes in clinically significant laboratory markers, measurement of pharmacodynamic parameters (including markers of angiogenesis), and assessment of tumor response and serum tumor markers. Patients were hospitalized at least from one day before motesanib administration and discharged after day 1 (cycle 2). After being discharged, during cycles 2 and 3, patients visited the clinic every week (during cycle 2) or every 2 weeks (during cycle 3), at which time clinical and laboratory evaluations were performed.

Based on the results of a previously reported clinical study, the starting dose of motesanib (Amgen Inc., Thousand Oaks, CA) was 50 mg. Planned motesanib dosages were 50, 100, 125, and 150 mg. Intrapatient dose escalation was not allowed. The total study duration for each patient consisted of three cycles of 28 days per cycle. The first cycle consisted of dosing on day 1, no dosing on day 2, daily dosing from day 3 through day 21 (19 days of consecutive dosing) and 1 week off. During the first cycle, the first motesanib dose was followed by a 48-h PK assay and measurements of urinary motesanib. During the second and third cycles, dosing will occur daily for 28 consecutive days. Dosing in this study was intended to continue for three cycles but was discontinued if disease progression was observed. If a DLT developed, administration was interrupted, and thereafter the decision to discontinue or restart was made by the investigator after the toxicity had resolved.

Three patients were initially enrolled in each cohort. If no patients experienced a DLT at the initial dose level, patients could be enrolled in the subsequent cohort. If a DLT occurred, an additional three patients could be enrolled at the current dose level to assess safety. If one patient experienced a DLT, the next dose level could be enrolled; if two or more patients experienced a DLT the next appropriate dose (increased or decreased) was determined by the principal investigator, Amgen, Inc., the study medical expert, and the study efficacy and safety evaluation committee. Additional patients could be enrolled in each cohort to further evaluate safety. Treatment with motesanib continued for up to 12 weeks (i.e., three treatment cycles). However, patients could choose to continue receiving motesanib until disease progression or unacceptable toxicity occurred.

Motesanib was also withheld when ANC was $<0.5 \times 10^9$/l. Treatment with motesanib could resume at the level of the immediately preceding dose cohort at the discretion of the investigator. Patients in the 50 mg QD cohort could restart at a dose of 25 mg QD. Patients who

required >2 weeks to recover from a DLT, experienced a second DLT, or who had cardiotoxicity meeting the DLT criteria were withdrawn from the study.

Dose-limiting toxicities and maximum tolerated dose

In this study, DLTs were defined as any treatment-related grade 3 or 4 nausea, diarrhea, or vomiting despite maximum supportive care; grade 3 or 4 neutropenia with fever >38.5°C; grade 3 fatigue, persistent for ≥7 days; grade 4 hypertension; or AST or ALT >300 IU/l; any other grade 3 or 4 non-hematologic toxicity; or any other grade 4 hematologic toxicity occurring during the first cycle. The MTD was defined as the highest dose level at which the incidence of DLTs was <33% of patients enrolled in the cohort.

Pharmacokinetics

Intensive pharmacokinetic analysis was performed for all patients on days 1 and 21 of the first treatment cycle. Plasma samples were taken predose and at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 24, and 48 h postdose (the 48-h collection was performed on day 1 only). Aliquots of plasma were prepared for analysis using solid phase extraction and motesanib concentrations were measured by a liquid chromatography–tandem mass spectrometry method using d3-motesanib as an internal standard. Two versions of a validated method were utilized having calibration curve ranges of 0.200–100 ng/ml for the 50 mg QD cohort and 0.500–100 ng/ml for other cohorts. Pharmacokinetic parameters of motesanib including observed maximum plasma concentration (C_{max}), time of maximum observed plasma concentration (t_{max}), area under the concentration versus time curve (AUC), and terminal elimination half-life ($t_{1/2,z}$) were calculated by non-compartmental analysis using WinNonlin software (Version 4.1e, Pharsight Corporation, Mountain View, CA).

Safety

Adverse events and their relationship to treatment were recorded throughout the study. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (version 3.0). Urinalysis and assessments of hematologic function, coagulation, and clinical chemistry were performed up to four times each cycle.

Efficacy

Tumors were measured by magnetic resonance imaging or computed tomography at a maximum of 4 weeks before study day 1 and at approximately 8-week intervals during the study. Tumor responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) [19].

Exploratory analysis of markers of angiogenesis

Serum samples for measurement of markers of angiogenesis were collected on study days 1 and 22 and at the end of the study. Serum concentrations of placental growth factor (PlGF), basic fibroblast growth factor (bFGF), VEGF, soluble KDR (sKDR), Flt-1, and soluble c-Kit were measured using a multiplexed sandwich immunoassay technique (Meso Scale Discovery (Gaithersburg, MD)).

Statistical analyses

Descriptive statistics are provided for each endpoint by cohort. The safety analysis population consisted of all patients who received at least one dose of motesanib. Dose–response relationships of the changes in biomarkers were analyzed by the regression models using *F*-test. Analyses were performed using SAS (Version 8.2, SAS Institute Inc., Cary, NC).

Results

Patient characteristics

A total of 15 patients were screened for eligibility between September 2004 and May 2005; all were subsequently enrolled in the study and received at least one dose of motesanib. Baseline demographic and clinical characteristics are summarized in Table 1. Of the patients enrolled, 9 (60%) were women; the median age was 55 years, and the median weight was 52 kg. Thirteen patients had received prior chemotherapy and two had received prior radiotherapy. All 15 patients discontinued treatment with motesanib. Fourteen patients discontinued motesanib treatment early due to disease progression and one patient discontinued due to an adverse event. No patients died during the study. Patients received motesanib for a median of 77 days (range 19–583).

Dose escalation, dose-limiting toxicities, and maximum tolerated dose

No dose-limiting toxicities were observed in patients enrolled in the 50 mg QD cohort, or the 100 mg QD cohort, or in the initial three patients enrolled in the 125 mg QD cohort. The 125 mg QD dose was previously established as the MTD in a similarly designed study conducted in the US [20]. Consequently, it was decided not to exceed a dose of 125 mg QD in this study. To further assess safety at this

Table 1 Baseline demographic and clinical characteristics

	Motesanib dose cohort			All patients (n = 15)
	50 mg QD (n = 3)	100 mg QD (n = 3)	125 mg QD (n = 9)	
Women, n (%)	2 (67)	1 (33)	6 (67)	9 (60)
Median age, years (range)	65 (45–71)	68 (46–69)	51 (32–72)	55 (32–72)
Median weight, kg (range)	37 (32–65)	48 (47–61)	55 (36–76)	52 (32–76)
Eastern Cooperative Oncology Group score, n (%)				
0	2 (67)	1 (33)	5 (56)	8 (53)
1	1 (33)	2 (67)	4 (44)	7 (47)
Tumor type, n				
Sarcoma	0	1	3	4
Gastrointestinal stromal tumor	0	0	3	3
Colorectal	1	1	0	2
Bile duct	1	0	0	1
Hilar cholangiocarcinoma	0	0	1	1
Lung	0	1	1	2
Stomach	1	0	0	1
Thymoma	0	0	1	1
Prior chemotherapy, n				
0	0	0	2	2
1	0	1	1	2
2	2	1	3	6
≥3	1	1	3	5
Prior radiotherapy, n				
0	3	2	8	13
2	0	1	1	2

dose level, six additional patients were enrolled in the 125 mg QD cohort. Again, no DLTs occurred. The 150 mg QD cohort was not evaluated, since the recommended dose was decided based on the results from the previous study conducted in the US [20] and this study. Therefore, the MTD was not reached in this study.

Safety

The most frequently reported treatment-emergent adverse events (with a patient incidence of at least 10%) during cycle 1 by preferred term were hypertension (47%), protein urine present (33%), blood urine present (20%), constipation (20%), cough (20%), fatigue (20%), headache (20%), white blood cell count decreased (20%), alanine aminotransferase increased (13%), aspartate aminotransferase increased (13%), blood triglycerides increased (13%), diarrhea (13%), dry skin (13%), eyelid edema (13%), hypoesthesia (13%), nausea (13%), pyrexia (13%), rash (13%), stomach discomfort (13%), and vomiting (13%) (Table 2).

All 15 patients enrolled in the study experienced treatment-related adverse events (Table 3). The most frequently occurring motesanib-related adverse events were proteinuria (n = 10, 67%), hypertension (n = 9, 60%), fatigue (n = 7, 47%), headache (n = 6, 40%), hematuria (n = 5, 33%), and diarrhea (n = 5, 33%). Two patients in the 100 mg QD dose cohort experienced grade 3 motesanib-related hypertension. In one patient motesanib treatment was interrupted due to hypertension, which resolved within 15 days after antihypertensive treatment started. In all other instances, hypertension was managed by administration of antihypertensive therapy alone. No patient enrolled in the study experienced either a grade 4 adverse event or a serious motesanib-related adverse event. One patient in the 50 mg QD cohort withdrew from the study due to grade 3 anorexia that was considered to be unrelated to motesanib treatment.

Pharmacokinetics

Evaluable plasma samples for pharmacokinetic analysis were available from all 15 patients during cycle 1. Motesanib was rapidly absorbed following single-dose oral administration, with a median t_{max} of between 0.25 and 1.0 h across the three dose cohorts. Similar t_{max} values were obtained following multiple-dose administration of motesanib

Table 2 Treatment-emergent adverse events occurring in at least 10% of patients (cycle 1)

Adverse event	Motesanib dose cohort			All patients ($n = 15$)
	50 mg QD ($n = 3$)	100 mg QD ($n = 3$)	125 mg QD ($n = 9$)	
Number of patients reporting adverse events, *n*	3	3	7	13
Hypertension	0	3	4	7
Protein urine present	2	1	2	5
Blood urine present	0	1	2	3
Constipation	0	1	2	3
Cough	0	1	2	3
Fatigue	1	1	1	3
Headache	0	1	2	3
White blood cell count decreased	0	1	2	3
Alanine aminotransferase increased	0	1	1	2
Aspartate aminotransferase increased	0	1	1	2
Blood triglycerides increased	0	1	1	2
Diarrhea	1	0	1	2
Dry skin	0	1	1	2
Eyelid edema	0	1	1	2
Hypoesthesia	0	0	2	2
Nausea	0	1	1	2
Pyrexia	0	0	2	2
Rash	0	0	2	2
Stomach discomfort	2	0	0	2
Vomiting	1	1	0	2

(i.e., day 21). Pharmacokinetic parameters of motesanib on days 1 and 21 are summarized in Table 4 and mean plasma motesanib concentration versus time profiles are shown in Fig. 1. The median of $t_{1/2}$ values ranged from 6.0 to 7.3 h after single-dose administration and from 3.8 to 4.8 h after multiple-dose administration, whereas these values did not appear to be dose dependent. The mean C_{max}, and $AUC_{0\text{-}24}$, values were approximately proportional to dose. However, these values were similar or slightly lower on day 21 than on day 1, indicating that there was no accumulation after daily administration.

Efficacy

All 15 patients were evaluable for antitumor response. No complete or partial responses per RECIST were observed (Table 5). All evaluable patients achieved stable disease. Five patients had durable (>24 weeks) stable disease: one patient with non-small-cell lung cancer (duration: 465 days), one patient with a gastrointestinal stromal tumor (duration: 175 days), one patient with a thymoma (duration: 252 days), one patient with malignant hemangiopericytoma (duration: 175 days) and one patient with alveolar soft part sarcoma (duration 539 days). All patients with durable stable disease were enrolled in the 125 mg QD dose cohort. Motesanib showed promising antitumor activity (all stable disease) in this study. The response duration for alveolar soft part sarcoma and non-small cell lung cancer patients were 539 and 465 days, respectively.

Analysis of proangiogenic markers

Several angiogenic markers such as VEGF, PlGF, bFGF, sFlt-1, sKDR, and c-Kit were determined in association with motesanib exposure. As shown in Fig. 2, change in sKDR from baseline was inversely related to dose and showed statistical significance ($R^2 = 0.275$; $p = 0.045$). In addition, changes in c-Kit from baseline was inversely related to dose and showed statistical significance ($R^2 = 0.449$; $p = 0.006$). However; changes in VEGF, PlGF, bFGF, and sFlt-1 did not show a statistically significant ($p > 0.05$) correlation with motesanib exposure (data not shown).

Discussion

Inhibition of angiogenesis has recently emerged as an effective therapy for solid tumors. Motesanib is an orally administered small-molecule antagonist inhibitor of VEGFR1, 2, 3; PDGFR, and c-Kit and has demonstrated antiangiogenic