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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

Table 3 Patient incidence of motesanib-related adverse events occurring in more than 10% of patients

Adverse event	Motesanib dose cohort			All patients (n = 15)
	50 mg QD (n = 3)	100 mg QD (n = 3)	125 mg QD (n = 9)	
Incidence of motesanib-related adverse events, n	3	3	9	15
Proteinuria	3	2	5	10
Hypertension	0	3	6	9
Fatigue	2	1	4	7
Headache	0	2	4	6
Hematuria	1	2	2	5
Diarrhea	1	0	4	5
Alanine aminotransferase increased	0	1	2	3
Dry skin	0	1	2	3
Nausea	0	1	2	3
Stomach discomfort	2	0	1	3
Vomiting	1	1	1	3
White blood cell count decreased	0	1	2	3
Aspartate aminotransferase increased	0	1	1	2
Blood alkaline phosphatase increased	0	0	2	2
Blood creatinine phosphokinase MB increased	1	1	0	2
Blood triglycerides increased	0	1	1	2
Cough	0	1	1	2
Eosinophil count increased	0	0	2	2
Eyelid edema	0	1	1	2
Edema	0	0	2	2
Pleural effusion	0	1	1	2
Rash	0	0	2	2
Weight decreased	1	0	1	2

and antitumor activity in preclinical models of human cancer [17] and acceptable toxicity and promising clinical efficacy in a phase 1 study conducted in the US [18].

The aim of this study was to investigate the safety, pharmacokinetics, and antitumor efficacy of motesanib in Japanese patients with advanced solid tumors.

No DLTs occurred in this study and, therefore, the MTD was not reached. We confirmed the tolerance of the 125 mg QD dose recommended in the US [18].

The safety profile of motesanib in this population of Japanese patients was similar to that observed in the US study [18].

Adverse events were typically mild to moderate in severity, and all of toxicities were acceptable at all motesanib doses tested in this study.

The most frequently occurring non-hematologic toxicity in cycle 1 was hypertension. There were two patients with grade 3 hypertension in level 2. The median time to onset of hypertension was 9 days (cycle 1) after treatment initiation. Hypertension increased in frequency as well as in severity at high dose or with multiple doses of motesanib. However, hypertension was typically manageable with antihypertensive therapy medications including calcium blocker.

The incidence of hypertension in this study was similar to that observed in the motesanib phase 1 study conducted in the US [18] as well as the incidence rate noted in studies of other VEGF inhibitors [20, 21]. Hypertension has been observed during treatment with other VEGF inhibitors and is considered a class effect of these agents [22]. Hypertension appears to be induced possibly by increasing vascular resistance (due to decreased NO and prostacyclin production), vascular rarefaction, and increased arterial stiffness [23, 24].

No patients experienced thromboembolic events or cholecystitis in this study.

Motesanib was rapidly absorbed following oral administration.

Values for t_{max} and $t_{1/2,z}$ were similar to those observed at the same doses in the US study [18]. However, exposure

Table 4 Pharmacokinetic parameters for motesanib following single-dose (day 1) and multiple-dose (day 21) oral administration

	Motesanib dose cohort		
	50 mg QD	100 mg QD	125 mg QD
Day 1			
n	3	3	9
t_{max}, h	0.25 (0.25–0.25)	0.5 (0.5–1.0)	1.0 (0.25–2.0)
C_{max}, ng/ml	462 (322–695)	521 (468–696)	792 (285–2410)
$t_{1/2,z}$, h	5.96 (5.07–6.12)	7.26 (6.35–9.24)	6.54 (4.04–8.11)
AUC_{0-inf}, μg h/ml	1.84 (1.17–1.88)	3.50 (1.56–5.85)	3.08 (2.35–6.61)
AUC_{0-24}, μg h/ml	1.77 (1.12–1.78)	3.16 (1.52–5.08)	2.84 (2.23–6.51)
CL/F, l/h	27.2 (26.6–42.7)	28.6 (17.1–64.1)	40.6 (18.9–53.1)
C_{24}, ng/ml	8.49 (6.83–12.5)	29.4 (3.53–50.2)	14.6 (4.68–37.0)
C_{48}, ng/ml	0.347 (0.310–0.715)	3.66 (0.547–11.3)	1.63 (BQL–4.94)
Day 21			
n	3	3	9
t_{max}, h	0.5 (0.5–2.0)	1.0 (1.0–2.0)	1.0 (0.25–2.0)
C_{max}, ng/ml	561 (267–669)	390 (351–636)	639 (272–1350)
$t_{1/2,z}$, h	3.81 (3.38–5.24)	4.83 (4.20–5.92)	4.12 (2.81–5.29)
AUC_{0-inf}, μg h/ml	NR	NR	NR
AUC_{0-24}, μg h/ml	1.31 (0.932–1.43)	2.36 (1.06–4.94)	1.99 (0.862–5.68)
CL/F, l/h	38.1 (35.0–53.6)	42.3 (20.2–94.6)	62.8 (22.0–145)
C_{24}, ng/ml	2.22 (1.24–4.64)	12.2 (2.81–45.3)	6.32 (0.979–33.8)
C_{48}, ng/ml	NR	NR	NR

AUC_{0-inf} = area under the plasma concentration versus time curve from time 0 to infinite time; AUC_{0-24} = area under the plasma concentration versus time curve from time 0–24 h postdose; CL/F = apparent clearance; C_{max} = maximum observed concentration after dosing; C_{24} = observed concentration at 24 h postdose; C_{48} = observed concentration at 48 h postdose; NR = not reported; QD = daily dose; t_{max} = time of maximum observed plasma concentration; $t_{1/2,z}$ = estimated terminal elimination half-life; BQL = below quantitation limit (0.5 ng/ml); All values are reported as the median (range)

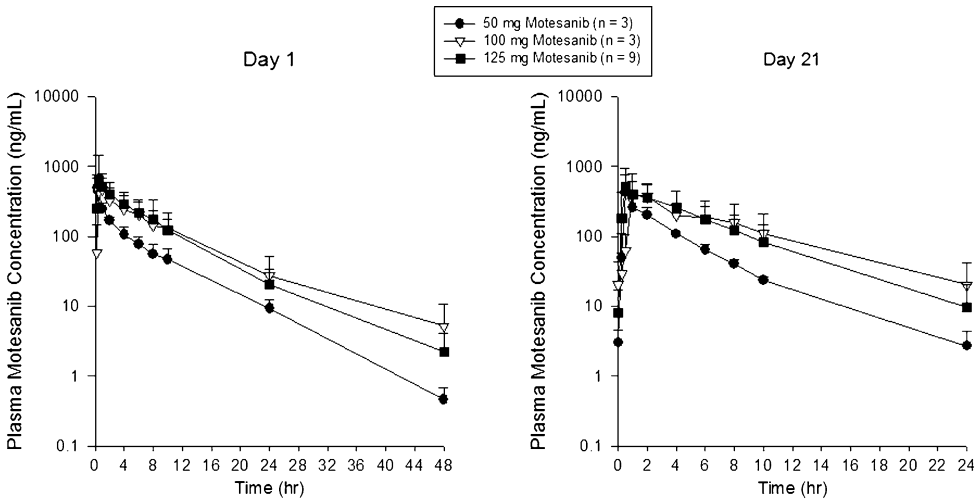

Fig. 1 Mean (+SD) plasma concentration–time profiles for motesanib after single-dose (day 1) and multiple-dose (day 21) administration in patients with advanced solid tumors

to motesanib was somewhat greater in this study than in previous motesanib studies. The reasons for this increased exposure are unclear.

Motesanib mean trough concentrations (C_{24}) were above the IC50 for human umbilical vein endothelial cell proliferation (4 ng/ml) [17] at dose ≥100 mg QD.

There was no evidence that motesanib accumulates in plasma following multiple-dose administration.

Motesanib exhibited encouraging antitumor activity in this study with all patients enrolled achieving a best response of stable disease. The duration of response in these patients seemed clinically meaningful. However,

Table 5 Tumor response per RECIST

	Motesanib dose cohort			All patients (n = 15)
	50 mg QD (n = 3)	100 mg QD (n = 3)	125 mg QD (n = 9)	
Patients with measurable/non-measurable disease at baseline, n	3	3	9	15
Response assessment, n				
Stable disease	3	3	9	15
Durable (>24 weeks) stable disease	0	0	5	5

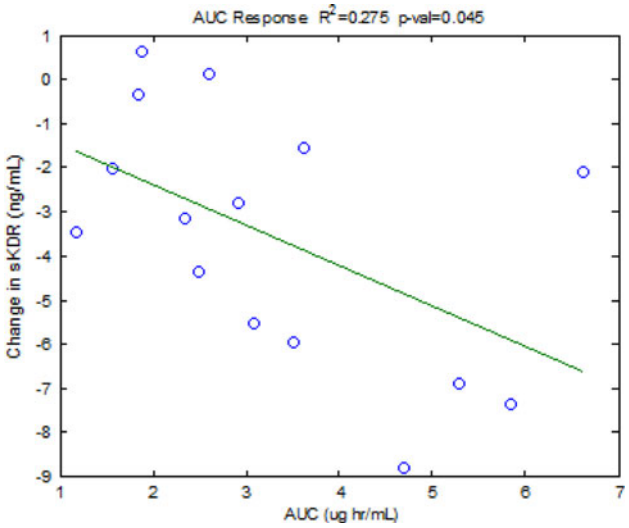

Fig. 2 Changes in serum sKDR compared to motesanib AUC

because of the small size of the study population, few firm conclusions can be drawn from this study regarding the clinical efficacy of motesanib. Bevacizumab, sunitinib malate, and sorafenib tosylate have demonstrated clinical efficacy, providing proof of concept that antiangiogenic agents can provide significant clinical benefit. In addition, multiple other small-molecule multikinase inhibitors including VEGFR as a target are currently under clinical development.

Adverse events generally reported to occur with increased incidence in patients receiving these investigational products include diarrhea, nausea, vomiting, hypertension, and fatigue [21, 25–27]. Some angiogenesis inhibitors have been associated with arterial and venous thrombosis [28, 29]. In this study, thrombosis was not observed.

The trends in the changes in the angiogenic cytokines follows patterns similar to those reported in the motesanib phase 1 study as reported in Rosen et al. [18]. These discrepancies could be associated with small sample size, and it should be taken the small sample size and paucity of decreased SLD measures into consideration at evaluation. The statistical analysis of the changes in the angiogenic factors in this study was limited by the small study size (15 patients). The results reported by Rosen et al. [18] were analyzed in larger study size of 69 patients.

Factors that may impact the comparison between the two studies are ethnicity, particular selection of tumor types, and the difference in when the tumor was assessed.

These results demonstrated that motesanib was tolerable in Japanese patients at doses up to 125 mg QD.

The safety profile of motesanib was similar to that observed in a US study.

These results, and the encouraging antitumor activity observed in this study, support the further development of motesanib for the treatment of patients with solid tumors.

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