Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

Cancer Therapy: Clinical

Clinical Cancer Research

Phase 1b Study of Motesanib, an Oral Angiogenesis Inhibitor, in Combination with Carboplatin/Paclitaxel and/or Panitumumab for the Treatment of Advanced Non–Small Cell Lung Cancer

George R. Blumenschein, Jr.[1], Karen Reckamp[2], G. Joe Stephenson[3], Timothy O'Rourke[4], Gregory Gladish[1], Jesse McGreivy[5], Yu-Nien Sun[5], Yining Ye[5], Mandy Parson[5], and Alan Sandler[6]

Abstract

Purpose: Motesanib is a small-molecule antagonist of vascular endothelial growth factor receptor 1, 2, and 3, platelet-derived growth factor receptor, and Kit. This phase 1b study assessed the safety, maximum tolerated dose (MTD), and pharmacokinetics, and explored the objective response of motesanib plus carboplatin/paclitaxel and/or the fully human anti–epidermal growth factor receptor monoclonal antibody panitumumab in advanced non–small cell lung cancer (NSCLC).

Experimental Design: Patients with unresectable NSCLC received sequentially escalating doses of motesanib [50, 125 mg once daily; 75 mg twice daily] orally continuously plus carboplatin/paclitaxel (arm A; first line) or panitumumab (arm B; first and second line) once every 21-day cycle or 125 mg once daily plus carboplatin/paclitaxel and panitumumab (arm C; first line).

Results: Forty-five patients received motesanib. Three dose-limiting toxicities occurred: grade 4 pulmonary embolism (n = 1; arm A, 50 mg once daily) and grade 3 deep vein thrombosis (n = 2; arm A, 125 mg once daily; arm C). The MTD was 125 mg once daily. Common motesanib-related adverse events were fatigue (60% of patients), diarrhea (53%), hypertension, (38%), anorexia (27%), and nausea (22%). Three cases of cholecystitis occurred but only in the 75-mg twice-daily schedule, which was subsequently discontinued. At 125 mg once daily, motesanib pharmacokinetics were not markedly changed with carboplatin/paclitaxel coadministration; however, exposure to paclitaxel was moderately increased. The objective response rates were 17%, 0%, and 17% in arms A, B, and C, respectively.

Conclusions: Treatment with motesanib was tolerable when combined with carboplatin/paclitaxel and/or panitumumab, with little effect on motesanib pharmacokinetics at the 125-mg once daily dose level. This dose is being investigated in an ongoing phase 3 study in NSCLC. *Clin Cancer Res; 16(1); 279–90.*

In the United States, non–small cell lung cancer (NSCLC) accounts for nearly 85% of lung cancer cases (1), with most patients presenting with locally advanced (stage III) or metastatic (stage IV) disease (2). Although 15% to 40% of patients initially respond to cytotoxic chemotherapy, which remains the primary therapeutic option, long-term prognosis is poor: standard-of-care treatment of advanced NSCLC with carboplatin in combination with paclitaxel yields response rates of 17% to 25%, with a median survival time of ~8 months (3, 4). Although a number of new, third-generation cytotoxic therapies have become available, improvements in outcomes for patients with advanced disease remain modest (5), suggesting that conventional treatment may have reached an effectiveness plateau.

Vascular endothelial growth factor (VEGF) through activation of its receptors VEGFR1 and VEGFR2 is a potent proangiogenic factor and a key mediator of neovascularization (6) in normal and malignant tissue (7). Platelet-derived growth factor is thought to play a role in angiogenesis by regulating vascular survival (8) and, in NSCLC, by increasing expression of VEGF (9). Several studies have shown that elevated VEGF and high microvessel density are associated with poor prognosis in NSCLC (10–13) and that VEGF may be associated with the promotion of malignant pleural effusion and pleural dissemination (14, 15).

In a separate signaling pathway, epidermal growth factor receptor (EGFR) directly promotes tumor growth and survival by regulating angiogenesis and apoptosis and by

Authors' Affiliations: [1]The University of Texas M.D. Anderson Cancer Center, Houston, Texas; [2]City of Hope Comprehensive Cancer Center, Duarte, California; [3]Cancer Center of the Carolinas, Greenville, South Carolina; [4]Spectrum Health, Grand Rapids, Michigan; [5]Amgen Inc., Thousand Oaks, California; and [6]Oregon Health Sciences University, Portland, Oregon

Corresponding Author: George R. Blumenschein, Jr., The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: 713-792-6363; Fax: 713-796-8655; E-mail: gblumens@mdanderson.org.

doi: 10.1158/1078-0432.CCR-09-1675

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

Translational Relevance

Non–small cell lung cancer (NSCLC) remains a significant therapeutic challenge. Most patients present with advanced or metastatic disease at initial diagnosis, and traditional, chemotherapy-based treatment provides limited benefit. Targeted therapies blocking the pathways involved in tumor growth and survival, such as the vascular endothelial growth factor and the epidermal growth factor receptor pathway, have emerged as important alternative treatment options. Added benefit may be achieved by combining targeted therapies with chemotherapy. Motesanib is a small-molecule antagonist of the vascular endothelial growth factor receptors 1, 2, and 3, and of platelet-derived growth factor and Kit receptors. This phase 1b study in patients with advanced NSCLC shows that treatment with motesanib plus carboplatin/paclitaxel with or without the fully human anti–epidermal growth factor receptor monoclonal antibody panitumumab was tolerable, with pharmacokinetic characteristics supporting 125-mg once-daily dosing of motesanib as combination therapy. By blocking multiple signaling pathways, motesanib may represent a novel targeted treatment approach for advanced NSCLC.

increasing expression of VEGF (16, 17). Expression of EGFR mRNA in tumor tissue from patients with NSCLC has been correlated with survival (18).

VEGF and its receptors as well as the EGFR signaling cascade are now two validated molecular targets for the development of novel treatment options for patients with advanced NSCLC, as shown in the Eastern Cooperative Oncology Group study E4599 (19), the Avastin in Lung (AVAIL) study (20), and the First-Line Treatment for Patients with EGFR-expressing Advanced NSCLC (FLEX) study (21). Currently, the anti-VEGF monoclonal antibody bevacizumab in combination with carboplatin and paclitaxel is approved for the first-line treatment of advanced or metastatic nonsquamous NSCLC (19); the EGFR inhibitor erlotinib is approved for second- or third-line treatment of NSCLC (22). Other antiangiogenic agents have been evaluated as first-line treatment in the setting of advanced NSCLC but thus far have failed to show improved clinical outcomes (23, 24).

Motesanib is an orally administered small-molecule antagonist of VEGFR1, 2, and 3; the platelet-derived growth factor receptor; and stem cell factor receptor (Kit; ref. 25). In monotherapy studies, motesanib has shown acceptable toxicity and promising antitumor activity in patients with advanced solid malignancies (26, 27). Preclinical studies have shown improved antitumor activity of motesanib against NSCLC-derived tumor xenografts when combined with panitumumab (Amgen Inc., data on file), a fully human anti-EGFR antibody approved for the treatment of third-line metastatic colorectal cancer (28). Clinical studies have suggested that combined VEGF and EGFR inhibition can improve outcomes in patients with advanced NSCLC (29, 30). The aim of the present study was to assess the safety and pharmacokinetics and to evaluate the efficacy of motesanib in the treatment of NSCLC when combined with cytotoxic chemotherapy and/or panitumumab.

Materials and Methods

Patients. Eligible adult (≥18 y) patients had histologically confirmed, unresectable stage IIIB or stage IV NSCLC with measurable or evaluable (nonmeasurable) disease per Response Evaluation Criteria in Solid Tumors (RECIST; ref. 31). Patients either were chemotherapy-naïve (arm A and C) or had received no more than one prior chemotherapy regimen for NSCLC (arm B). Other key inclusion criteria were Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of ≥3 mo, and adequate hematologic, renal, and hepatic function. Key exclusion criteria were symptomatic or untreated central nervous system metastases requiring concurrent treatment; large (≥3 cm) central tumor lesions (located adjacent to or within the hilum or mediastinum) of squamous cell histology unless treated by central irradiation; uncontrolled hypertension; history of arterial or venous thrombosis, bleeding diathesis, pulmonary hemorrhage, gross hemoptysis, or ischemic heart disease; systemic chemotherapy, radiation therapy, or antibody therapy within 14, 21 d, or 6 wk of study enrollment, respectively; or treatment with any anti-VEGF or anti-EGFR therapy. All patients provided written informed consent before any study-related procedures were done.

Study design. This was a multicenter (conducted in six centers in the United States), open-label, dose-finding, phase 1b study of motesanib (Amgen Inc.) administered in combination with carboplatin/paclitaxel as first-line treatment (arm A), with panitumumab as second-line treatment (arm B), or with carboplatin/paclitaxel and panitumumab as first-line treatment (arm C) in patients with advanced NSCLC. Primary end points were the incidence of treatment-related adverse events and dose-limiting toxicities (DLT) and determination of the motesanib pharmacokinetic profile in the three treatment arms. Secondary end points included paclitaxel and motesanib exposure [maximum observed plasma concentration (C_{max}) and area under the concentration-time curve (AUC)] when motesanib and carboplatin/paclitaxel were administered 30 min and ~48 h apart, panitumumab exposure when coadministered with carboplatin/paclitaxel or motesanib plus carboplatin/paclitaxel (arms B and C), and the objective response rate in each treatment arm.

Arms A and B tested escalating doses of motesanib up to 125 mg orally once daily, which had been established as the maximum tolerated dose (MTD) in a previous monotherapy setting in advanced solid tumors (26), or at 75 mg twice daily. Dose cohorts in arms A and B enrolled concurrently, and once dose escalation was completed, arm C started enrollment to test motesanib at a

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

dose established to be tolerable in arms A and B. In each of the three treatment arms, six patients were planned to be enrolled per dose cohort.

The study protocol and all study-related procedures were approved by each site's Institutional Review Board. To verify adherence to the protocol, monitoring visits to each study center were conducted on an approximate monthly basis. The study monitor had access to all study-related records. The ClinicalTrials.gov registration number for this study is NCT00094835.

Treatment and dose escalation. In arm A, patients received motesanib orally at escalating doses of 50 mg once daily, 125 mg once daily, or 75 mg twice daily starting on day 3 of cycle 1, and then from day 1 of each subsequent cycle until disease progression or intolerability occurred. Paclitaxel was given concomitantly through a 3-h i.v. infusion at 200 mg/m^2, and carboplatin was given through a 30-min i.v. infusion at an area under the AUC of 6 mg/mL · min. Carboplatin/paclitaxel was administered once on day 1 of each 21-d cycle for up to six cycles (in the absence of disease progression). Thereafter, patients received motesanib alone if no disease progression or drug intolerance occurred.

In arm B, patients received motesanib orally beginning on day 3 at escalating doses at 50 mg once daily, 125 mg once daily, or 75 mg twice daily plus panitumumab 9 mg/kg through i.v. infusion on day 1 of each 21-d cycle. This dose was modeled to achieve a panitumumab trough concentration comparable with the one reached with the 2.5-mg/kg dose given once weekly, which, in combination with paclitaxel/carboplatin, was found to be tolerable in patients with advanced NSCLC (32). The dose of panitumumab was reduced to 4.5 mg/kg in the event of a grade ≥3 skin-related toxicity. If the reduced dose was tolerated for one cycle, it could be escalated to 7 mg/kg.

In arms A and B, dose escalation occurred when greater than or equal to four of the planned six patients in the current cohort completed one cycle without experiencing a DLT (defined below). A single intrapatient dose escalation to the highest tolerable dose was allowed. In the event of a DLT, motesanib was withheld and resumed with a 25-mg-per-dose reduction if toxicity resolved to grade 1 or reached the patient's baseline value. Patients were withdrawn from the study if motesanib was withheld for >3 wk.

In arm C, patients received 125 mg once daily motesanib orally plus carboplatin/paclitaxel beginning on day 3 (dose and schedule as described in arm A) and panitumumab (9 mg/kg through i.v. infusion on day 1 of each 21-d cycle). Enrollment in arm C started after the 125-mg once daily dose had been established as safe and tolerable in treatment arms A and B. There was no dose escalation in arm C. Carboplatin/paclitaxel treatment and panitumumab dosing followed the same rules as outlined for arms A and B, respectively.

Adverse event assessment and management. Adverse events were recorded and classified according to the Medical Dictionary for Regulatory Activities. Severity was graded according to the Common Terminology Criteria for Adverse Events version 3.0 of the National Cancer Institute. DLTs were defined as grade 3 fatigue persistent for ≥7 d; grade 3 or 4 nausea, diarrhea, and vomiting despite maximum supportive care; grade 3 or 4 neutropenia with fever >38.5°C; grade 4 neutropenia (absolute neutrophil count, $<0.5 \times 10^9$/L) for >7 d; grade 4 thrombocytopenia (platelet count, $<25.0 \times 10^9$/L); grade 4 anemia; grade 4 hypertension; aspartate aminotransferase or alanine aminotransferase of >10 times the upper limit of normal; grade 4 rash/desquamation; or any other treatment-related grade 3 or 4 adverse event occurring during the first cycle.

Use of antihypertensive medications to control blood pressure was permitted. Motesanib was discontinued if hypertension persisted or if patients experienced cholecystitis or symptomatic gallbladder enlargement; treatment was withheld for at least 1 wk if patients experienced grade 3 or 4 asymptomatic thrombosis.

Pharmacokinetic analyses. Plasma samples for intensive pharmacokinetic analysis of motesanib were collected predose and at 0.25, 0.5, 1, 2, 4, 6, and 24 h (immediately before the next morning dose) after administration of motesanib on day 3 of cycle 1 and day 1 of cycle 2. Additional samples from the twice daily cohorts were collected at 12 (immediately before the second daily dose), 12.5, 13, 14, and 16 h on day 3 of cycle 1 and day 1 of cycle 2. The concentration of motesanib in plasma was assessed using a validated liquid chromatography/tandem mass spectrometry assay (CEDRA Clinical Research, LLC) with a lower limit of quantification of 0.500 ng/mL. Plasma samples for paclitaxel intensive pharmacokinetic analysis were collected predose; at the completion of infusion; and 0.5, 2.5, 6.5, 24, and 48 h after infusion on day 1 of cycles 1 and 2. The concentration of paclitaxel in plasma was analyzed using a validated liquid chromatography/tandem mass spectrometry assay (BASi Northwest Laboratory, Inc.) with a lower limit of quantitation of 0.100 ng/mL. Serum samples for the measurement of panitumumab concentrations were collected predose on day 1 of cycles 1 to 4 and at the completion of infusion on day 1 of cycles 1 to 3. Panitumumab concentrations were measured using a validated ELISA (Amgen Inc., data on file) with a lower limit of quantitation of 400 ng/mL. Patients who received motesanib and had evaluable plasma data were included in pharmacokinetic analyses using standard noncompartmental methods and WinNonlin software version 4.1e (Pharsight Corporation). To assess the impact of motesanib administration on paclitaxel exposure, geometric least square means (GLSM) and the ratio of GLSM between cycle 2 and cycle 1 were calculated for C_{max} and AUC values using the SAS PROC MIXED procedure (SAS for Windows, version 9.1, WIN_PRO platform; SAS Institute, Inc.). Specifically, GLSM were calculated by obtaining the least squares means for the log-transformed C_{max} and AUC values ($logC_{max}$ and logAUC) for cycle 2 and cycle 1 and then converting it back to their original scale. The ratio of GLSM with a 90% confidence interval (CI) was calculated by estimating the difference (and 90% CI) in the least squares means between cycle 2 and cycle 1 for $logC_{max}$ and logAUC and then converting

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

it back to their original scale. Only patients with available data for both cycle 1 and cycle 2 were included in the GLSM analysis.

Assessment of tumor response. In patients with measurable or evaluable disease (based on imaging studies), tumor response was assessed by either computed tomography or magnetic resonance imaging scans performed within 4 wk of enrollment, at week 9, and every 9 wk (±1 wk) thereafter, regardless of treatment cycle, or immediately if disease progression was suspected. Tumor responses were evaluated by investigators using RECIST (31). Complete or partial responses were confirmed by computed tomography or magnetic resonance imaging no less than 4 wk after the initial response. A best tumor response of stable disease required patients to be stable for ≥50 d.

Statistical analysis. The initial study size selected was 85 patients, which would allow meeting the primary end point of incidence of adverse events and clinical laboratory abnormalities defined as DLTs by providing a 92% probability of observing a rare adverse event (i.e., an adverse event with a frequency of 10%). The safety analysis set consists of all patients who received at least one dose of motesanib. The efficacy analysis set consists of all patients who received at least one dose of motesanib (arm A) or at least one dose of motesanib and panitumumab (arms A and C). Progression-free survival was calculated as the number of days between the first day of protocol-specified treatment and the date when disease progression was determined or the date when death occurred. Duration of response was calculated as the number of days between the date when an objective response that was subsequently confirmed occurred and the date when relapse was determined or death of any cause occurred. All data were analyzed using SAS software version 8.2 (SAS Institute, Inc.). Statistical analysis of the data was completed on August 20, 2007.

Results

Patients. Between January 2005 and September 2006, 45 patients were enrolled in the study and received at least one dose of motesanib (arm A, $n = 23$; arm B, $n = 16$; arm C, $n = 6$). Demographics and baseline characteristics are summarized in Table 1. Across treatment arms, most patients were men (64%) and current or former smokers (82%). Eighty-two percent of patients had advanced metastatic (stage IV) disease per investigator assessment, and most patients (91%) had one or more sites of disease. The most common histologic cancer subtype was adenocarcinoma (27 patients, 60%); two patients (4%) had squamous histology. Patients in treatment arms A and C were chemotherapy-naïve per inclusion criteria (Table 1). All patients discontinued treatment with motesanib because of the following reasons: disease progression (42% of patients), adverse events (40%), administrative decision (13%), and withdrawal of consent (4%). Twenty-seven patients (60%) completed the safety follow-up; overall median follow-up time was 16 weeks (range, 3-51 weeks).

Dose escalation, DLTs, and MTD. In arm A (motesanib plus carboplatin/paclitaxel), six patients received a motesanib starting dose of 50 mg once daily. One DLT of grade 4 pulmonary embolism, considered serious, occurred in the second enrolled patient; the remaining five patients completed the first treatment cycle without experiencing a DLT. Six patients were then enrolled into the next cohort and the motesanib dose was escalated to 125 mg once daily. No DLTs occurred. To support further development of the 125-mg once daily dosing regimen, which had been established as the MTD for motesanib monotherapy (26), an additional five patients were enrolled in this dose cohort to allow for a methodical review of clinical safety data. One DLT of grade 3 deep vein thrombosis occurred among these five patients. Subsequently, a final cohort of six patients was enrolled, with dose escalation to 75 mg twice daily. No DLTs occurred in this group. In arm B, four patients initially received motesanib 50 mg once daily plus panitumumab. No DLTs occurred in this cohort and dose escalation to 125 mg once daily (seven patients; the sixth and seventh patient were screened and found eligible at the same time) and 75 mg twice daily (five patients) continued. There were no DLTs reported in either of these two cohorts. In both arms A and B, the 75-mg twice daily dose cohort was discontinued after an increased risk of cholecystitis was observed with that dose (the twice daily cohort in arm B was discontinued early before enrollment of a sixth patient). In arm C, six patients received motesanib 125 mg once daily plus carboplatin/paclitaxel and panitumumab. One DLT of grade 3 deep vein thrombosis occurred. Based on the dose escalation results, the motesanib MTD was established as 125 mg once daily administered continuously. Because the primary objective of the study had been met and additional studies specifically investigating the safety and efficacy of motesanib plus carboplatin/paclitaxel had been initiated, enrollment was stopped before the planned sample size of 85 patients was reached.

Across treatment arms, median time on motesanib treatment was 11.6 weeks (range, 1-46 weeks); the median daily dose was 125 mg (range, 25-150 mg). In treatment arm A, patients received a median of four cycles of carboplatin/paclitaxel (range, 1-6) and, in arm C, a median of 3.5 cycles (range, 1-6). Seven patients (26%) in arm A and one patient (17%) in arm C completed the protocol-specified six cycles of carboplatin/paclitaxel treatment. Patients in arm A received 98.7% and 100% of the full intended dose of carboplatin and paclitaxel, respectively; patients in arm C received 100% and 90.5% of the full intended dose of carboplatin and paclitaxel, respectively. One patient each had at least one carboplatin (arm A) or paclitaxel (arm C) dose interruption, respectively. Patients treated with panitumumab received a median of 3.5 infusions (range, 1-12) in arm B and 3.5 infusions (range, 1-6) in arm C. Eight patients (18%) had at least one motesanib dose reduction (arm A, B, C: $n = 4, 3, 1$, respectively) mostly due to adverse events ($n = 6$; arm A, B, C: $n = 2, 3, 1$, respectively).

Adverse events. Across treatment arms, 42 patients (93%) experienced at least one motesanib-related adverse event. Among these, grade 3 adverse events occurred in

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

Table 1. Patient demographic and baseline characteristics

Characteristic	Arm A (*n* = 23)	Arm B (*n* = 16)	Arm C (*n* = 6)
Sex, no. (%)			
Women	7 (30)	6 (38)	3 (50)
Men	16 (70)	10 (63)	3 (50)
Median age, y (range)	64 (39-79)	58 (32-76)	60 (56-64)
Race, no. (%)			
White	22 (96)	14 (88)	5 (83)
Black	1 (4)	1 (6)	0 (0)
Asian	0 (0)	1 (6)	1 (17)
Disease stage, no. (%)			
Stage IIIB	4 (17)	3 (19)	1 (17)
Stage IV	19 (83)	13 (81)	5 (83)
No. of sites of disease,* no. (%)			
0	2 (9)	2 (13)	0 (0)
1	19 (83)	11 (69)	5 (83)
2	2 (9)	3 (19)	1 (17)
Histologic subtype, no. (%)			
Adenocarcinoma	12 (52)	10 (63)	5 (83)
Bronchoalveolar carcinoma	0 (0)	1 (6)	0 (0)
Large cell carcinoma	2 (9)	0 (0)	0 (0)
Squamous cell carcinoma	1 (4)	1 (6)	0 (0)
Other	8 (35)	4 (25)	1 (17)
ECOG performance status, no. (%)			
0	8 (35)	4 (25)	1 (17)
1	15 (65)	12 (75)	5 (83)
Median time since initial diagnosis, y (range)	0.1 (0-3.9)	0.7 (0.1-3.7)	0.1 (0-0.1)
Time since last prior therapy, mo (range)	0.7 (0.5-15.1)	3.7 (0.5-213.0)	0 (0)
Prior therapy for lung cancer,† no. (%)			
Any therapy	10 (43)	15 (94)	0 (0)
Prior chemotherapy	0 (0)	14 (88)	0 (0)
Prior radiotherapy	4 (17)	8 (50)	0 (0)
Prior other therapy	6 (26)	6 (38)	0 (0)
Tobacco use, no. (%)			
Never	4 (17)	4 (25)	0 (0)
Former	16 (70)	9 (56)	6 (100)
Current	3 (13)	3 (19)	0 (0)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*As assessed by investigator.

†Includes all therapies for lung cancer received before study enrollment.

65% (arm A), 50% (arm B), and 33% (arm C) of patients, most commonly fatigue (arm A/B: 50 mg once daily, 17%/0%; 125 mg once daily, 27%/29%; 75 mg twice daily, 33%/20%) and hypertension (arm A/B: 50 mg once daily, 33%/0%; 125 mg once daily, 27%/29%; 75 mg twice daily, 17%/40%), or fatigue and headache (arm C; Table 2). A total of five patients (11%) experienced grade 4 motesanib-related adverse events (see below), which occurred more frequently in arm C than in the other two treatment arms. No motesanib-related grade 5 adverse events were reported.

Several adverse events of interest considered related to motesanib treatment were noted (Table 2). Three patients had acute cholecystitis; all events were grade 3, were rated serious, and occurred in patients receiving motesanib 75 mg twice daily in arm A ($n = 1$) and arm B ($n = 2$). Six patients (13%) developed motesanib-related pulmonary embolism. All of these events occurred in arm A (50 mg once daily, $n = 3$; 75 mg twice daily, $n = 1$) and in arm C ($n = 2$), and were either grade 3 (one event in arm A, 50 mg once daily) or grade 4 (the remaining five events) in severity. Three of the pulmonary embolisms were considered serious (arm A, 50 mg once daily, $n = 2$; arm C, $n = 1$), and in five instances, pulmonary embolism led to study discontinuation. There were two patients who had pulmonary embolism and thrombosis (arm A, 50 mg once daily and arm C; $n = 1$ each). Two patients developed grade 3 deep vein thrombosis (arm

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

A, 125 mg once daily and arm C, $n = 1$ each). Of the described thromboembolic events, only three events occurred within the first treatment cycle and therefore were considered DLTs (pulmonary embolism, $n = 1$ and deep vein thrombosis, $n = 2$; see above). Nine patients experienced hemorrhagic adverse events including serious grade 3 gastrointestinal hemorrhage ($n = 1$) and grade 1 urinary tract hemorrhage (Table 2); both occurred in the 75-mg twice daily cohort of arm A. All other bleeding events were of worst grade 1 and occurred either in the 125-mg once daily or the 75-mg twice daily cohorts. There were no grade 4 or 5 hemorrhagic events, and neither of the two patients with squamous cell histology experienced hemorrhagic events.

All 22 patients who received panitumumab experienced panitumumab-related adverse events. Those that occurred in ≥10% of patients were fatigue (27%; grade 3, 7%), dermatitis acneiform (29%; no grade 3), hypomagnesemia (24%; grade 3, 4%), pruritus (24%; no grade 3), diarrhea (22%; grade 3, 2%), nausea (16%; no grade 3); (13% each) anorexia (grade 3, 2%), epistaxis (no grade 3), exfoliative rash (no grade 3), myalgia (grade 3, 2%), and stomatitis (no grade 3); and erythema (11%; no grade 3). Three patients had grade 4 panitumumab-related events of hypomagnesemia (arm B, two patients) and pulmonary embolism (arm C, one patient). Adverse events of specific interest related to panitumumab treatment included grade 3 deep vein thrombosis (one patient; arm C), dry skin (three patients; no grade 3), paronychia (three patients; no grade 3), and acne (two patients; no grade 3). Related grade 3 hypertension (two patients; arm B) and grade 3 cholecystitis

Table 2. Motesanib treatment–related adverse events occurring in ≥10% of patients and related adverse events of interest

Related adverse events, no. of patients (%)	Arm A ($n = 23$)			Arm B ($n = 16$)			Arm C ($n = 6$)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Patients with any related adverse event	21 (91)	15 (65)	3 (13)	15 (94)	8 (50)	0 (0)	6 (100)	2 (33)	2 (33)
Related adverse events occurring in ≥10% of patients									
Fatigue	12 (52)	6 (26)	0 (0)	11 (69)	3 (19)	0 (0)	4 (67)	1 (17)	0 (0)
Diarrhea	12 (52)	1 (4)	0 (0)	7 (44)	1 (6)	0 (0)	5 (83)	0 (0)	0 (0)
Hypertension	10 (43)	6 (26)	0 (0)	6 (38)	4 (25)	0 (0)	1 (17)	0 (0)	0 (0)
Anorexia	5 (22)	2 (9)	0 (0)	6 (38)	2 (13)	0 (0)	1 (17)	0 (0)	0 (0)
Nausea	4 (17)	0 (0)	0 (0)	4 (25)	0 (0)	0 (0)	2 (33)	0 (0)	0 (0)
Arthralgia	3 (13)	1 (4)	0 (0)	2 (13)	2 (13)	0 (0)	2 (33)	0 (0)	0 (0)
Headache	4 (17)	0 (0)	0 (0)	2 (13)	1 (6)	0 (0)	1 (17)	1 (17)	0 (0)
Weight loss	4 (17)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	2 (33)	0 (0)	0 (0)
Dyspnea	4 (17)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33)	0 (0)	0 (0)
Hypomagnesemia	4 (17)	0 (0)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	1 (4)	0 (0)	0 (0)	4 (25)	1 (6)	0 (0)	1 (17)	0 (0)	0 (0)
Pruritus	1 (4)	0 (0)	0 (0)	3 (19)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)
Myalgia	3 (13)	0 (0)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pain in extremity	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (67)	0 (0)	0 (0)
Dizziness	3 (13)	0 (0)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patients with related adverse events of interest									
Pulmonary embolism	4 (17)*	1 (4)	3 (13)	0 (0)	0 (0)	0 (0)	2 (33)*	0 (0)	2 (33)
Cholecystitis	1 (4)	1 (4)	0 (0)	2 (13)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)
Deep vein thrombosis	1 (4)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (17)	0 (0)
Thrombosis	1 (4)*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)*	1 (17)	0 (0)
Hemorrhage	3 (13)	1 (4)	0 (0)	3 (19)	0 (0)	0 (0)	3 (50)	0 (0)	0 (0)
Gastrointestinal	1 (4)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	2 (9)†	0 (0)	0 (0)	3 (19)‡	0 (0)	0 (0)	3 (50)§	0 (0)	0 (0)
Cardiac disorders	2 (9)‖	0 (0)	0 (0)	1 (6)¶	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*One patient experienced pulmonary embolism and thrombosis.
†Urinary tract hemorrhage and hemoptysis.
‡Epistaxis ($n = 2$) and hemoptysis.
§Epistaxis ($n = 2$) and hematuria.
‖Atrial fibrillation ($n = 1$) and conduction disorder ($n = 1$).
¶Atrial fibrillation ($n = 1$) and sinus tachycardia ($n = 1$).

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

Table 3. Pharmacokinetic parameters of motesanib when administered with or without carboplatin/paclitaxel

Parameter	Arm A		
	Cycle 1 (day 3, –CP)	Cycle 2 (day 1, +CP)	Cycle 2 to Cycle 1
	Mean ± SD	Mean ± SD	GLSM ratio (90% CI)
50 mg once daily	(*n* = 3-4)	(*n* = 2-4)	
t_{max},* h	0.75 (0.50-2.0)	1.5 (1.0-2.0)	
C_{max}, ng/mL	158 ± 55	148 ± 25	0.97 (0.57-1.66)
$t_{1/2,z}$, h	7.34 ± 2.07	4.98 ± NR†	
AUC,† μg·h/mL	0.971 ± 0.300	1.05 ± NR‡	NE
$C_{24\ h}$, ng/mL	9.12 ± 4.17	5.61 ± NR‡	
125 mg once daily	(*n* = 7-9)	(*n* = 5-9)	
t_{max},* h	1.0 (0.5-6.0)	1.0 (0.5-4.0)	
C_{max}, ng/mL	525 ± 250	748 ± 701	0.98 (0.48-2.01)
$t_{1/2,z}$, h	5.33 ± 1.05	6.41 ± 2.08	
AUC,† μg·h/mL	3.21 ± 1.12	4.50 ± 2.62	1.42 (0.89-2.26)
$C_{24\ h}$, ng/mL	26.5 ± 16.8	43.4 ± 44.8	
75 mg twice daily	(*n* = 5-6)	(*n* = 5-6)	
$t_{max(0\text{-}12\ h)}$,* h	0.75 (0.25-1.0)	0.63 (0.25-4.0)	
$C_{max(0\text{-}12\ h)}$, ng/mL	448 ± 112	390 ± 319	
$t_{1/2,z(0\text{-}12\ h)}$, h	5.77 ± 1.45	6.36 ± 1.70	
$AUC_{0\text{-}24\ h}$, μg·h/mL	2.91 ± 1.01	3.11 ± 2.38	
$C_{24\ h}$, ng/mL	56.7 ± 27.4	45.4 ± 35.9	

Abbreviations: $AUC_{0\text{-}24\ h}$, AUC from time 0-24 h; $C_{24\ h}$, plasma concentration at 24 h; NE, not estimated because only one subject had AUC data for cycles 1 and 2; NR, not reported; $t_{1/2,z}$, estimated terminal phase half-life; t_{max}, time at which maximum plasma concentration was observed.

*t_{max} and $t_{max(0\text{-}12\ h)}$ are reported as a median (range) value.

†For once daily cohorts, $AUC_{0\text{-}\infty}$ is reported for cycle 1 and $AUC_{0\text{-}24}$ is reported for cycle 2.

‡SD not reported if $n < 3$.

(one patient; arm B) were also reported. No grade 5 panitumumab-related events occurred.

Treatment discontinuation due to adverse events was greater in arm C (67% of patients) and arm A (48%) than in arm B (25%). Similarly, the incidence of motesanib-related serious adverse events was generally higher in treatment arm C (33%) and arm A (26%) than in arm B (19%). Two on-study deaths occurred: one (on study day 167) was attributed to worsening clinical interstitial pulmonary fibrosis (arm A) and the other (on study day 20) to progression of NSCLC (arm B). Neither event was considered related to treatment by the investigator.

Pharmacokinetics. Pharmacokinetic parameters of motesanib as administered per treatment arm A are summarized in Table 3. After oral administration of single or multiple doses, motesanib was rapidly absorbed, with overall median values of time to C_{max} ranging from 0.75 to 1.0 hours. Values of motesanib C_{max}, $AUC_{0\text{-}\infty}$, and plasma concentration at 24 hours (C_{24}) on day 3 of cycle 1 (48 hours after carboplatin/paclitaxel administration) were similar to those that had previously been reported in a monotherapy study (26). A few outlying values (2-fold above/below SD) were observed, likely because of interpatient variability and limited sample sizes (all outlying values were included in the analysis). After administration of motesanib twice daily, C_{max} was lower but the value for C_{24} was higher compared with once daily administration of 125 mg across cycles and segments (data not shown). In treatment arm A, motesanib pharmacokinetic profiles (Fig. 1) and the ratio point estimates and 90% CIs for the GLSM values of C_{max} and AUC for cycle 2 (motesanib plus carboplatin/paclitaxel) relative to cycle 1 (motesanib alone; Table 3) suggest that coadministration of carboplatin/paclitaxel did not markedly change motesanib exposure in all three dose groups. Similar results were observed for arms B and C (data not shown).

After i.v. infusion, paclitaxel disposition showed a fast distribution phase with rapidly declining concentrations, followed by a slower terminal elimination phase (Fig. 1). The paclitaxel ratio point estimates and 90% CIs for the GLSM values for cycle 2 (motesanib plus carboplatin/paclitaxel) relative to cycle 1 (carboplatin/paclitaxel alone) were 1.26 (1.10-1.44) for C_{max} (n = 21) and 1.24 (1.11-1.39) for AUC (n = 21) in treatment arm A, and 1.31 (0.56-3.07) for C_{max} (n = 3) and 1.32 (0.71-2.43) for AUC

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

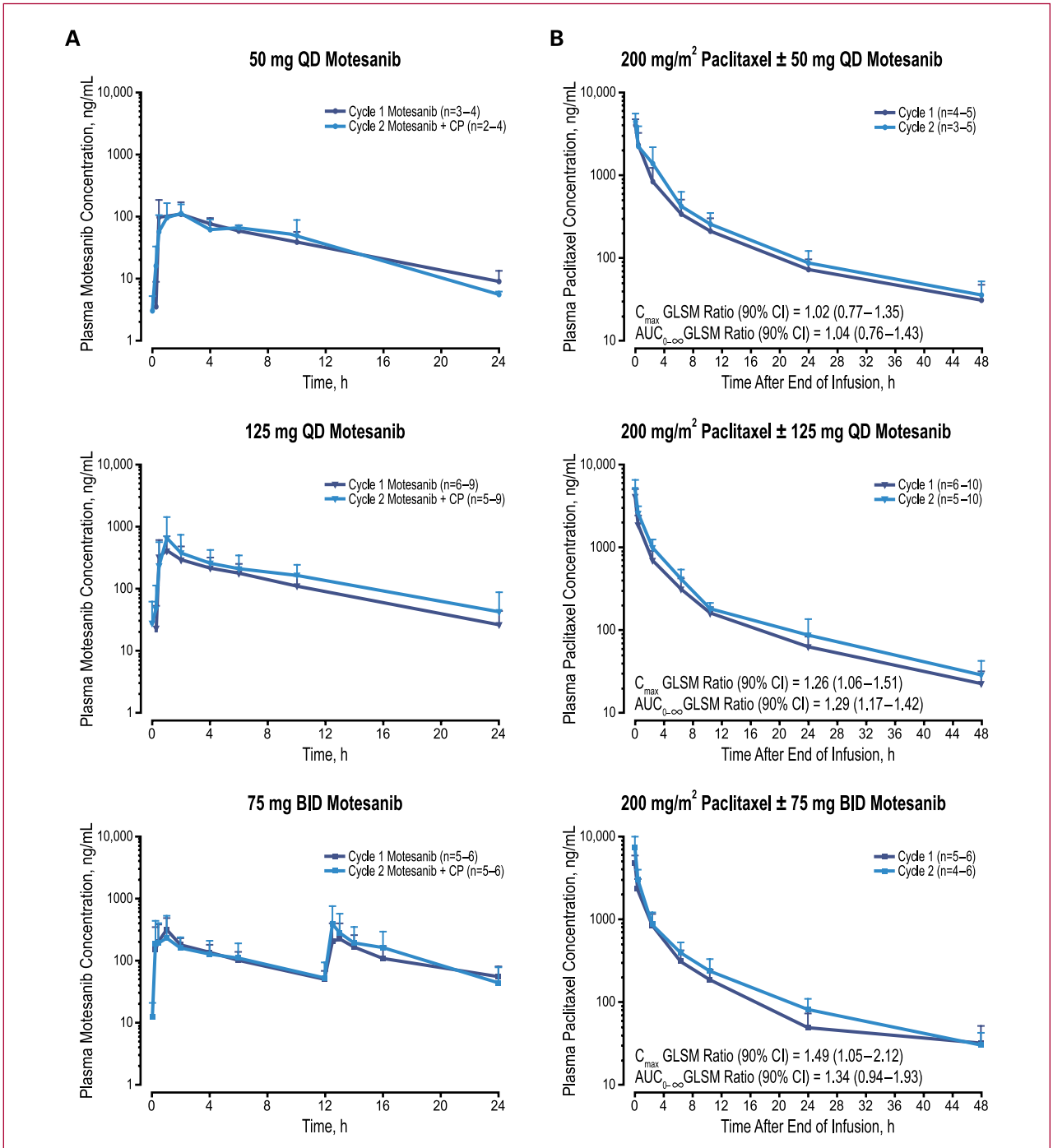

Fig. 1. Pharmacokinetic profile of (*A*) motesanib 30 min or 48 h after administration with and without carboplatin/paclitaxel (*CP*) in treatment arm A and (*B*) paclitaxel after administration with and without motesanib in treatment arm A. $AUC_{0-\infty}$, AUC from 0 to infinity; GLSM, log-transformed geometric least square mean.

($n = 3$) in arm C. The data suggest that coadministration with motesanib resulted in a slight increase in paclitaxel C_{max} and AUC values. In arm A, the paclitaxel GLSM ratios seemed to be dose dependent, and the ratios for the 125-mg once daily dose cohort were similar to those observed in arm C at the same dose level (Fig. 1). Concentrations of panitumumab in the serum were consistent with the expected peak and trough values at steady state (data not shown).

Tumor response. Forty-two patients (93%) had measurable disease at baseline (Table 4). Three patients (7%) had

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

Table 4. Best tumor response per RECIST and investigator assessment through at least week 9

Response assessment, *n* (%)	Arm A (*n* = 23)	Arm B (*n* = 16)	Arm C (*n* = 6)
Patients with measurable disease at baseline	22 (96)	14 (88)	6 (100)
Overall response (CR + PR)	4 (17)	0 (0)	1 (17)
Confirmed CR	0 (0)	0 (0)	0 (0)
Confirmed PR	4 (17)	0 (0)	1 (17)
Stable disease	11 (48)	9 (56)	2 (33)
Progressive disease	3 (13)	5 (31)	2 (33)
Disease control (CR + PR + stable disease)	15 (65)	9 (56)	3 (50)
Unevaluable patients*	3 (13)	1 (6)	0 (0)
Patients without available response data†	2 (9)	1 (6)	1 (17)

Abbreviations: CR, complete response; PR, partial response.
*Patients with a response assessment before week 9, without a subsequent assessment.
†No post baseline tumor measurements available.

evaluable disease [two achieved stable disease (arm B) and one achieved durable stable disease (arm A)]. At the end of the study, four patients (17%) in arm A and one patient (17%) in arm C had achieved a confirmed partial response per investigator based on RECIST. There were no confirmed complete or partial responses in treatment arm B. Forty-eight percent of patients in arm A and 56% in arm B had stable disease as their best tumor response compared with 33% in arm C. Overall, the disease control rate (objective response or stable disease) was 65%, 56%, and 50% in arms A, B, and C, respectively. The proportion of patients with disease progression was lowest in treatment arm A (13%). Of the 38 patients with available tumor measurements, 27 (71%) experienced a decrease from baseline in the sum of longest diameters of target lesions (Fig. 2).

In treatment arm A, 9 of 23 patients (39%) had progression-free survival events (disease progression or death). The Kaplan-Meier estimate (95% CI) of the median progression-free survival time per investigator in arm A was

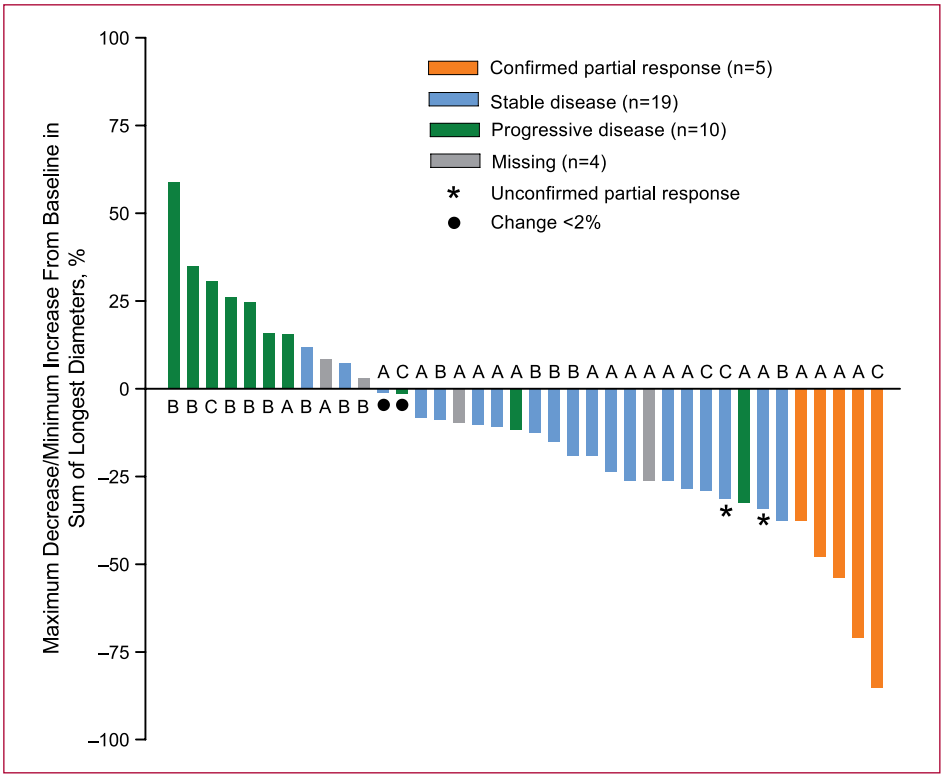

Fig. 2. Maximum change from baseline in the sum of longest diameters of target lesions (per RECIST and investigator assessment). Not shown: stable disease, *n* = 3 (arm A, *n* = 1; arm B, *n* = 2; nonmeasurable disease at baseline). Missing: post baseline tumor measurement was done before week 9, without a subsequent confirmatory assessment (no best tumor response assessment available). A, B, C, treatment arm A, B, or C.

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

27 weeks (23-39 weeks). Of the five patients who had a confirmed partial response, three had no assessment of disease progression (censored) and two patients (arm A, 125-mg once daily cohort and arm C, respectively) subsequently progressed. The duration of response for the three censored patients was 29+, 10+, and 5+ weeks; the duration of response for the two patients who subsequently progressed was 12 and 10 weeks.

Discussion

To date, the most promising new therapeutic options for patients with NSCLC are combination therapies using an antiangiogenic treatment plus cytotoxic chemotherapy. By targeting two aspects of tumor development, cell proliferation, and vascularization, additional antitumor efficacy may be gained. Two studies of bevacizumab plus erlotinib have shown that blocking both the VEGF and EGFR pathways simultaneously resulted in encouraging clinical efficacy in the treatment of NSCLC (29, 30).

In the current phase 1b study, patients with advanced NSCLC received motesanib as first-line (arm A and C) or first- and second-line (arm B) treatment either in combination with carboplatin/paclitaxel, with the anti-EGFR antibody panitumumab, or with carboplatin/paclitaxel plus panitumumab. The motesanib MTD was established as 125 mg once daily given continuously, which is consistent with data reported in the motesanib phase 1 monotherapy study in solid tumors (26). The 75-mg twice daily dosing was associated with three serious events of grade 3 cholecystitis, leading to discontinuation of this cohort. Thus far, only one other study with the VEGFR inhibitor sunitinib has reported occurrences of cholecystitis (33). Based on the dose escalation data, motesanib 125 mg once daily given continuously is the recommended dose for future studies.

Coadministration of carboplatin/paclitaxel (with or without panitumumab) did not markedly change motesanib exposure compared with data from the above-mentioned phase 1 monotherapy study (26). The results are also in agreement with data from other combination studies that showed little effect of coadministration of gemcitabine/cisplatin or FOLFIRI/FOLFOX with or without panitumumab on motesanib pharmacokinetics after repeat dosing of 125 mg once daily in patients with solid tumors or metastatic colorectal cancer, respectively (34, 35). C_{max} and AUC values for paclitaxel, which is partially metabolized by CYP3A4 through a secondary pathway (36), were increased by approximately 20% to 30% when coadministered with motesanib, a weak CYP3A4 inhibitor at 125 mg once daily (37). This effect was dose dependent, but whether it reflects the inhibitory action of motesanib on CYP3A4 at higher doses or data variability is currently unknown. Although the GLSM ratios for paclitaxel C_{max} and AUC in the 125-mg once daily cohort of arm C were similar to those in arm A at the same dose level, the effect of motesanib coadministration on paclitaxel exposure seemed to be less evident based on the respective 90% CIs. Overall, the paclitaxel exposure observed in this study remained within the range of or was lower than published pharmacokinetic data at a dose of 225 mg/m^2, which was well tolerated with other investigational therapies (38, 39).

Motesanib in combination with chemotherapy resulted in 17% of patients in arm A achieving partial response and 65% achieving disease control (complete response + partial response + stable disease). However, treatment-related thromboembolic events, which have previously been linked to VEGF(R) inhibitors (40), occurred at notable frequency throughout the study but only in arm A (5 of the 23 patients; two events were DLTs) and arm C (three of the six patients; one event was a DLT). The 50% patient incidence rate in arm C is difficult to interpret given the small *n* in this cohort. In contrast, the patient incidence rate seen in arm A (21.7%) is in line with the 17.6% patient incidence rate of thromboembolic events reported in a phase 2 study of bevacizumab 15 mg/kg with carboplatin/paclitaxel in first-line locally advanced or metastatic NSCLC (41). More robust information on the occurrence of such events with motesanib treatment in the setting of NSCLC is currently being collected in ongoing studies. Hypertension occurred frequently as is common to this class of agents, but could generally be controlled with antihypertensive medication, and there were no dose reductions or treatment discontinuations due to hypertension. Previous studies have noted an increased incidence of pulmonary hemorrhage, including life-threatening and fatal events, with bevacizumab treatment in patients with nonsquamous NSCLC (19, 29) and, to a much larger extent, in those with squamous NSCLC (41). In the present study, no pulmonary bleeding occurred that was considered a serious adverse event. Nine patients had hemorrhagic events related to motesanib treatment, mostly epistaxis, hemoptysis, and hematuria. All events but one (serious grade 3 gastrointestinal hemorrhage in arm A) were of worst grade 1 in severity. No pulmonary hemorrhage, bleeding, or hemoptysis was observed in the two patients with squamous histology enrolled in the study. Adverse events related to panitumumab treatment were generally consistent with previous reports (28, 42).

Although toxicity profiles across treatment groups were generally similar and manageable, a greater proportion of patients in arm C, however, discontinued the study or experienced treatment-related grade 4 events or thromboembolic events. Due to the small number of patients in this arm ($n = 6$) no informed conclusions can be reached, and the safety and efficacy of combining VEGF- and EGFR-targeting therapies with chemotherapy regimens in NSCLC remains to be investigated further.

In summary, the results from the present study show that motesanib at the established MTD of 125 mg once daily in combination with panitumumab or carboplatin/paclitaxel was tolerable, with favorable pharmacokinetics and evidence of tumor control. However, considering the small size of this study and the observed interpatient variability in motesanib exposure, the true effect of motesanib in this study is difficult to estimate. Larger studies are under way

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

to further evaluate the potential efficacy and tolerability of motesanib 125 mg once daily plus carboplatin/paclitaxel for the treatment of patients with advanced NSCLC.

Disclosure of Potential Conflicts of Interest

J. McGreivy, Y.-N. Sun, Y. Ye, and M. Parson are employees and shareholders in Amgen Inc.; G.R. Blumenschein, Jr., received commercial research support from Amgen Inc., Bayer, Pfizer, GSK Exelixis, and Merck, and has been a consultant for Amgen Inc., Bayer, and Abbott; K. Reckamp received commercial research support from Amgen Inc., Tragara Pharmaceuticals, OSI Pharmaceuticals, Pfizer, GSK, and Eli Lilly, and received honoraria from Genentech, and has been a consultant for Amgen Inc. and Tragara Pharmaceuticals; A. Sandler received commercial research support from Genentech and Bayer, received honoraria from Amgen Inc. and Genentech, and has been a consultant for Amgen Inc., Bayer, Pfizer, and Genentech, T. O'Rourke is the Betz Family Endowed Chair in Cancer at Spectrum Health, Grand Rapids, MI. G.J. Stephenson has been a consultant to Amgen Inc. The other authors have no conflicts of interest to declare.

Acknowledgments

We thank Rebeca Melara, MS (Amgen Inc.), for the pharmacokinetic data analysis, Cindy Wake, BS (Amgen Inc.), for the pharmacokinetic sample analysis, Ali Hassan, PhD, (whose work was funded by Amgen Inc.), and Beate Quednau, PhD (Amgen Inc.) for assistance in drafting this manuscript.

Grant Support

This study was funded by Amgen Inc.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 7/2/09; revised 10/15/09; accepted 10/20/09; published OnlineFirst 12/22/09.

References

1. Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer 1995;75:191–202.
2. Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. Chest 2005;128:452–62.
3. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–8.
4. Kelly K, Crowley J, Bunn PA, Jr., et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210–8.
5. Wakelee HA, Bernardo P, Johnson DH, Schiller JH. Changes in the natural history of nonsmall cell lung cancer (NSCLC)-comparison of outcomes and characteristics in patients with advanced NSCLC entered in Eastern Cooperative Oncology Group trials before and after 1990. Cancer 2006;106:2208–17.
6. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25:581–611.
7. Ferrara N. The role of vascular endothelial growth factor in pathological angiogenesis. Breast Cancer Res Treat 1995;36:127–37.
8. Song S, Ewald AJ, Stallcup W, Werb Z, Bergers G. PDGFRβ+ perivascular progenitor cells in tumours regulate pericyte differentiation and vascular survival. Nat Cell Biol 2005;7:870–9.
9. Shikada Y, Yonemitsu Y, Koga T, et al. Platelet-derived growth factor-AA is an essential and autocrine regulator of vascular endothelial growth factor expression in non-small cell lung carcinomas. Cancer Res 2005;65:7241–8.
10. Fontanini G, Vignati S, Boldrini L, et al. Vascular endothelial growth factor is associated with neovascularization and influences progression of non-small cell lung carcinoma. Clin Cancer Res 1997;3:861–5.
11. Yuan A, Yu CJ, Kuo SH, et al. Vascular endothelial growth factor 189 mRNA isoform expression specifically correlates with tumor angiogenesis, patient survival, and postoperative relapse in non-small-cell lung cancer. J Clin Oncol 2001;19:432–41.
12. Han H, Silverman JF, Santucci TS, et al. Vascular endothelial growth factor expression in stage I non-small cell lung cancer correlates with neoangiogenesis and a poor prognosis. Ann Surg Oncol 2001;8:72–9.
13. Fontanini G, Bigini D, Vignati S, et al. Microvessel count predicts metastatic disease and survival in non-small cell lung cancer. J Pathol 1995;177:57–63.
14. Yano S, Nishioka Y, Goto H, Sone S. Molecular mechanisms of angiogenesis in non-small cell lung cancer, and therapeutics targeting related molecules. Cancer Sci 2003;94:479–85.
15. Ishii H, Yazawa T, Sato H, et al. Enhancement of pleural dissemination and lymph node metastasis of intrathoracic lung cancer cells by vascular endothelial growth factors (VEGFs). Lung Cancer 2004;45:325–37.
16. Ciardiello F, Caputo R, Bianco R, et al. Inhibition of growth factor production and angiogenesis in human cancer cells by ZD1839 (Iressa), a selective epidermal growth factor receptor tyrosine kinase inhibitor. Clin Cancer Res 2001;7:1459–65.
17. Herbst RS, Bunn PA, Jr. Targeting the epidermal growth factor receptor in non-small cell lung cancer. Clin Cancer Res 2003;9:5813–24.
18. Brabender J, Danenberg KD, Metzger R, et al. Epidermal growth factor receptor and HER2-neu mRNA expression in non-small cell lung cancer is correlated with survival. Clin Cancer Res 2001;7:1850–5.
19. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.
20. Manegold C, von Pawel J, Zatloukal P, et al. Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704 [abstract]. J Clin Oncol 2007;25:LBA7514.
21. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525–31.
22. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–32.
23. Scagliotti G, von Pawel J, Reck M, et al. Sorafenib plus carboplatin/paclitaxel in chemonaive patients wtih stage IIIB-IV non-small cell lung cancer (NSCLC): interim analysis (IA) results from the phase III, randomized, double-blind, placebo-controlled, ESCAPE (Evaluation of Sorafenib, Carboplatin, and Paclitaxel Efficacy in NSCLC) Trial [abstract]. J Thorac Oncol 2008;3:S97–8.
24. Laurie SA, Arnold A, Shepherd FA, et al. National Cancer Institute of Canada Clinical Trials Group study BR.24, a randomized placebo

Published OnlineFirst December 22, 2009; DOI: 10.1158/1078-0432.CCR-09-1675

controlled phase II trial of cediranib (CED) plus carboplatin + paclitaxel (C+P) in advanced non-small cell lung cancer of any histology: further analyses [abstract]. J Thorac Oncol 2008;3:S304.
25. Polverino A, Coxon A, Starnes C, et al. AMG 706, an oral, multikinase inhibitor that selectively targets vascular endothelial growth factor, platelet-derived growth factor, and Kit receptors, potently inhibits angiogenesis and induces regression in tumor xenografts. Cancer Res 2006;66:8715–21.
26. Rosen LS, Kurzrock R, Mulay M, et al. Safety, pharmacokinetics, and efficacy of AMG 706, an oral multikinase inhibitor, in patients with advanced solid tumors. J Clin Oncol 2007;25:2369–76.
27. Sherman SI, Wirth LJ, Droz JP, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. N Engl J Med 2008;359:31–42.
28. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658–64.
29. Herbst RS, O'Neill VJ, Fehrenbacher L, et al. Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer. J Clin Oncol 2007; 25:4743–50.
30. Herbst RS, Johnson DH, Mininberg E, et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. J Clin Oncol 2005;23:2544–55.
31. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
32. Crawford J, Swanson P, Prager D, et al. Panitumumab, a fully human antibody, combined with paclitaxel and carboplatin versus paclitaxel and carboplatin alone for first line advanced non-small cell lung cancer (NSCLC): a primary analysis [abstract 1123]. Eur J Cancer Suppl 2005;3:324.
33. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516–24.
34. Crawford J, Burris H, Stephenson J, et al. Safety and pharmacokinetics (PK) of AMG 706 in combination with panitumumab and gemcitabine-cisplatin in patients (pts) with advanced cancer [abstract]. J Clin Oncol 2007;25:14057.
35. Tebbutt N, Burris H, Hurwitz H, et al. Safety and pharmacokinetics (PK) of motesanib diphosphate with or without panitumumab (pmab) plus FOLFIRI or FOLFOX for the treatment of metastatic colorectal cancer (mCRC) [abstract 468PD]. Ann Oncol 2008;19:viii155–6.
36. Rochat B. Role of cytochrome P450 activity in the fate of anticancer agents and in drug resistance: focus on tamoxifen, paclitaxel and imatinib metabolism. Clin Pharmacokinet 2005;44:349–66.
37. Yan L, Wong S, Wathen L, et al. The pharmacokinetic (PK) effect of AMG 706 on CYP3A activity evaluated by use of oral midazolam as probe in patients with advanced solid tumors [abstract]. J Clin Oncol 2005;23:3178.
38. Herbst RS, Madden TL, Tran HT, et al. Safety and pharmacokinetic effects of TNP-470, an angiogenesis inhibitor, combined with paclitaxel in patients with solid tumors: evidence for activity in non-small-cell lung cancer. J Clin Oncol 2002;20:4440–7.
39. Herbst RS, Hammond LA, Carbone DP, et al. A phase I/IIA trial of continuous five-day infusion of squalamine lactate (MSI-1256F) plus carboplatin and paclitaxel in patients with advanced non-small cell lung cancer. Clin Cancer Res 2003;9:4108–15.
40. Eskens FA, Verweij J. The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; a review. Eur J Cancer 2006;42:3127–39.
41. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184–91.
42. Berlin J, Posey J, Tchekmedyian S, et al. Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. Clin Colorectal Cancer 2007;6:427–32.

AACR American Association for Cancer Research

Clinical Cancer Research

Phase 1b Study of Motesanib, an Oral Angiogenesis Inhibitor, in Combination with Carboplatin/Paclitaxel and/or Panitumumab for the Treatment of Advanced Non–Small Cell Lung Cancer

George R. Blumenschein, Jr., Karen Reckamp, G. Joe Stephenson, et al.

Clin Cancer Res 2010;16:279-290. Published OnlineFirst December 22, 2009.