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International, Randomized, Placebo-Controlled, Double-Blind Phase III Study of Motesanib Plus Carboplatin/Paclitaxel in Patients With Advanced Nonsquamous Non–Small-Cell Lung Cancer: MONET1

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ABSTRACT

Purpose
We evaluated whether motesanib (a selective oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3; platelet-derived growth factor receptor; and Kit) combined with carboplatin/paclitaxel improved overall survival (OS) versus chemotherapy alone in patients with nonsquamous non–small-cell lung cancer (NSCLC) and in the subset of patients with adenocarcinoma.

Patients and Methods
Patients with stage IIIB/IV or recurrent nonsquamous NSCLC (no prior systemic therapy for advanced disease) were randomly assigned 1:1 to carboplatin (area under the curve, 6 mg/ml · min) and paclitaxel (200 mg/m^2) intravenously for up to six 3-week cycles plus either motesanib 125 mg (arm A) or placebo (arm B) once daily orally. OS was the primary end point. Secondary end points included progression-free survival (PFS), objective response rate (ORR), adverse events (AEs), and association between placental growth factor (PLGF) change and OS.

Results
A total of 1,090 patients with nonsquamous NSCLC were randomly assigned (arms A/B, n = 541 of 549); of those, 890 had adenocarcinoma (n = 448 of 442). Median OS in arms A and B was 13.0 and 11.0 months, respectively (hazard ratio [HR], 0.90; 95% CI, 0.78 to 1.04; $P = .14$); median OS for the adenocarcinoma subset was 13.5 and 11.0 months, respectively (HR, 0.88; 95% CI, 0.75 to 1.03; $P = .11$). In descriptive analyses (arms A *v* B), median PFS was 5.6 months versus 5.4 months ($P = < .001$); ORR was 40% versus 26% ($P < .001$). There was no association between PLGF change and OS in arm A. The incidence of grade ≥ 3 AEs (arms A and B, 73% and 59%, respectively) and grade 5 AEs (14% and 9%, respectively) was higher with motesanib treatment.

Conclusion
Motesanib plus carboplatin/paclitaxel did not significantly improve OS over carboplatin/paclitaxel alone in patients with advanced nonsquamous NSCLC or in the adenocarcinoma subset.

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INTRODUCTION

Two pivotal phase III trials have laid the foundation for using targeted antiangiogenic agents in the treatment of metastatic nonsquamous non–small-cell lung cancer (NSCLC). In the E4599 study, treatment with bevacizumab, an anti–vascular endothelial growth factor (VEGF) monoclonal antibody, combined with carboplatin/paclitaxel significantly improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) compared with carboplatin/paclitaxel alone.[1] In the AVAiL (AVAstin in Lung) study, bevacizumab plus cisplatin/gemcitabine improved PFS and ORR, compared with placebo, but not OS.[2,3]

Efforts to identify drugs that inhibit key signaling pathways involved in the pathogenesis of cancer have led to the development of multitargeted agents. Small-molecule tyrosine kinase inhibitors that block several kinases simultaneously may offer advantages over single-target agents.[4] Furthermore, there is interest in identifying patients most likely to respond to targeted therapies based on specific biomarkers[5] and/or tumor histology.[6]

Motesanib is a selective oral inhibitor of VEGF receptors (VEGFR) 1, 2, and 3; platelet-derived growth factor receptor; and Kit[7] that has demonstrated antitumor activity when administered as monotherapy[8-10] or combined with chemotherapy.[11] In a phase II randomized, open-label study in advanced nonsquamous NSCLC, ORR, PFS, and OS were estimated to be comparable among patients who received carboplatin/paclitaxel and either motesanib 125 mg once daily (n = 61) or bevacizumab 15 mg/kg once every 3 weeks (n = 63).[11] A biomarker analysis of that study showed significant associations between increase in placental growth factor (PLGF) during the first 3 weeks of treatment and efficacy outcomes in the motesanib 125-mg once daily arm.[12] PLGF is a VEGF homolog that can promote angiogenesis by activating VEGFR-1.[13]

The primary objective of the MONET1 (Motesanib NSCLC Efficacy and Tolerability) study was to determine whether motesanib combined with carboplatin/paclitaxel improved OS, compared with placebo plus carboplatin/paclitaxel, in patients with advanced nonsquamous NSCLC and in the subset of patients with adenocarcinoma histology. We also assessed whether increases in PLGF during motesanib treatment were associated with OS.

PATIENTS AND METHODS

Eligibility

Initially, the study enrolled patients with NSCLC of all histologies. After a planned review of data from 600 patients (including 223 with squamous histology) in November 2008, the independent data monitoring committee recommended that enrollment of all patients be halted and treatment of those with squamous histology be discontinued because of higher early mortality and a higher incidence of gross hemoptysis compared with placebo. Patients with nonsquamous histology continued to receive treatment. The study protocol was amended in April 2009 to only allow enrollment of patients with nonsquamous histology; enrollment resumed in June 2009. This article reports results from the amended study.

Eligible patients ($\geq$ 18 years of age) had histologically confirmed unresectable stage IIIB with pericardial/pleural effusion or stage IV/recurrent nonsquamous NSCLC; measurable or nonmeasurable disease per Response Evaluation Criteria in Solid Tumors (RECIST 1.0)[14]; Eastern Cooperative Oncology Group performance status $\leq$ 1; life expectancy $\geq$ 3 months; and adequate renal, cardiac, hepatic, and hematologic function. Key exclusion criteria were history of pulmonary hemorrhage or gross hemoptysis within 6 months of randomization; prior chemotherapy, including adjuvant chemotherapy within 52 weeks of randomization; symptomatic or untreated CNS metastases; adenosquamous histology or unclear histologic type (> 10% squamous cells); prior targeted therapy; uncontrolled hypertension; arterial or venous thrombosis within 12 months, or bleeding diathesis or bleeding within 14 days of randomization. Study procedures were approved by an independent ethics committee/institutional review board at each study site. All patients provided written informed consent.

Study Design and Treatments

The study was conducted at 198 centers in 32 countries. Patients received paclitaxel (200 mg/m^2) and carboplatin (area under the curve, 6 mg/ml · min) on day 1 of each 3-week cycle for up to six cycles and were randomly assigned 1:1 using a computerized interactive voice response system to also receive oral motesanib 125 mg once daily (arm A) or placebo (arm B). Randomization was stratified by disease stage (IIIB *v* IV/recurrent), weight loss in the previous 6 months before randomization (< 5% *v* $\geq$ 5%), sex (male *v* female), and prior adjuvant chemotherapy (yes *v* no). Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent.

In case of treatment-related grade 3 or 4 toxicity, motesanib/placebo was withheld until the toxicity resolved to grade $\leq$ 1 or baseline. Treatment could then be resumed with a 25-mg dose reduction but was permanently discontinued if more than two dose reductions were required or if grade 3 or 4 toxicity recurred after a dose delay and/or reduction or persisted for more than 3 weeks.

The primary end point was OS. Secondary end points included PFS (from randomization to disease progression per RECIST), ORR per RECIST 1.0, and incidence of adverse events (AEs). Before unblinding, the statistical analysis plan was amended to also assess association between motesanib treatment-induced PLGF change and OS as a secondary end point.

Assessments

Computed tomography/magnetic resonance imaging was performed every 6 $\pm$ 1 weeks for assessment of tumor response by investigators. Objective responses were confirmed $\geq$ 4 weeks after the initial response assessment. If symptoms suggestive of disease progression occurred, patients were evaluated for tumor response.

All AEs (from the start of treatment to 30 days after the last dose) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Biomarker Analysis

Serum samples were obtained before treatment on day 1 of cycles 1, 2, and 3 and every 6 weeks thereafter. Serum PLGF was quantified using a two-step chemiluminescent microparticle immunoassay (ARCHITECT; Abbott Laboratories, Abbott Park, IL). Briefly, serum sample and anti-PLGF antibody paramagnetic microparticles were incubated together; following a wash step, anti-PLGF acridinium-labeled antibody was added. After another incubation and wash, pretrigger and trigger solutions were added, and chemiluminescent signal was measured. The lower limit of quantitation was 3.4 pg/mL; the linear response range was 4 to 1,500 pg/mL.

Statistical Analysis

The study was designed to accrue approximately 1,060 patients with nonsquamous histology to have 80% power to detect a hazard ratio (HR) of 0.80 (12.5 months *v* 10 months) for OS with two-sided $\alpha = .03$ in the patients with nonsquamous histology. The study had 80% power to detect an HR of 0.77 (13 months *v* 10 months) for OS with two-sided $\alpha = .02$ in the adenocarcinoma subset. An α split testing strategy was used to control the overall type I error rate of the study. The primary analysis was planned at 742 and 593 deaths among patients with nonsquamous histology and the adenocarcinoma subset, respectively, whichever occurred later. An interim analysis was planned at 370 events among nonsquamous patients; early stopping guidelines are described in the study protocol (Data Supplement).

OS and PFS were compared between arms A and B using stratified log-rank tests based on the stratification factors at randomization. HRs for the effect of motesanib on OS and PFS between arms A and B were estimated using a stratified Cox proportional hazards model.[15] Difference in ORR between arms A and B was calculated with a stratified Cochran-Mantel-Haenszel test[15] using the randomization stratification factors. The association between motesanib treatment-induced PLGF change and OS was evaluated using a Cox model with the log-transformed fold-change in PLGF from baseline at week 4 as a continuous variable. If OS and PLGF were significantly associated, fold-change in PLGF was to be assessed based on a prespecified cutoff ($\geq$ 2.0-fold *v* < 2.0-fold change). A hierarchical testing scheme for the secondary efficacy end points (PFS, PLGF, and ORR) was specified if the primary end point (OS) was met.

Efficacy analyses for OS and PFS included all randomly assigned patients with nonsquamous histology following the intent-to-treat principle. Safety analyses included all randomly assigned patients who received one or more doses of motesanib/placebo. Biomarker analyses included all patients randomly assigned who had PLGF values at weeks 1 (baseline) and 4 and had received motesanib/placebo the day before the week 4 PLGF sample collection.

RESULTS

Patients

Between July 5, 2007, and March 18, 2010, 1,090 patients with nonsquamous NSCLC were randomly assigned to motesanib (n = 541; arm A) or placebo (n = 549; arm B). Before the protocol amendment, the study also enrolled 360 patients with squamous histology. Data from this cohort will be reported in a separate publication. Eighteen patients with nonsquamous NSCLC did not receive motesanib (n = 10) or placebo (n = 8; Fig 1). Most patients had adenocarcinoma histology (arm A, 83%; arm B, 81%), weight loss less than 5% in the previous 6 months, and stage IV/recurrent disease (Table 1). Clinical characteristics were generally balanced across treatment arms.

Treatment

Median daily doses of motesanib or placebo were 125 mg in both treatment arms. Patients received motesanib for a median of 4.1 months (range, 0.03 to 35.9 months) and placebo for 4.1 months (range, 0.03 to 31.5 months). Carboplatin was administered for a median of 4.5 cycles (range, one to six cycles) in arm A and 5.0 cycles (range, one to six cycles) in arm B; paclitaxel was administered for a median of 4.0 cycles (range, one to six cycles) in arm A and 5.0 cycles (range, one to six cycles) in arm B. At the time of this analysis, 519 patients (96%) in arm A and 534 patients (97%) in arm B had discontinued motesanib/placebo; more patients in arm A than arm B had discontinued for reasons other than disease progression (Fig 1). Median follow-up times were 11 months (range, 0.2 to 41 months) in arm A and 10 months (range, 0.2 to 38 months) in arm B.

OS

Treatment with motesanib did not significantly improve OS. At the time of this analysis, 66% of patients in arm A and 72% in arm B had died. Among all patients with nonsquamous histology, median OS times were 13.0 months (95% CI, 11.2 to 14.0 months) in arm A versus 11.0 months (95% CI, 10.1 to 12.4 months) in arm B (HR, 0.90; 95% CI, 0.78 to 1.04; $P = .14$; Fig 2A). In the adenocarcinoma subset, median OS time was 13.5 months (95% CI, 11.3 to 14.7 months) in arm A versus 11.0 months (95% CI, 9.9 to 12.4 months) in arm B (HR, 0.88; 95% CI, 0.75 to 1.03; $P = .11$; Fig 2B). Prespecified subgroup analyses suggested longer survival among patients receiving motesanib who were nonwhite (HR, 0.76; 95% CI, 0.59 to 0.97; n = 375) or who were enrolled outside the United States/Canada/Australia/European Union (HR, 0.77; 95% CI, 0.61 to 0.98; n = 414; Fig 3).

PFS

Among all patients with nonsquamous histology, median PFS times were 5.6 months in arm A versus 5.4 months in arm B (HR, 0.79; 95% CI, 0.68 to 0.90; $P = < .001$; Fig 4A). PFS times in the adenocarcinoma

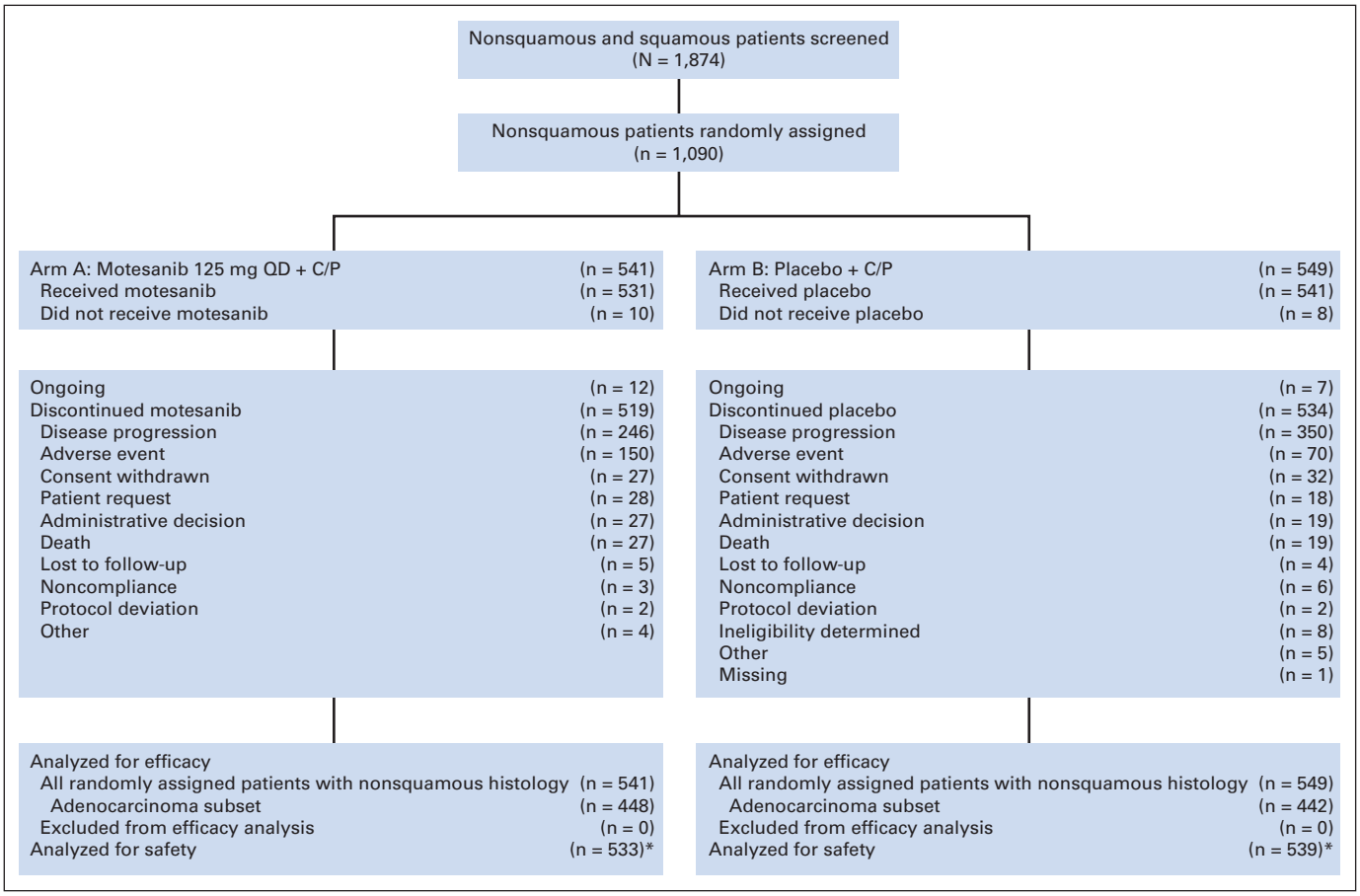

Fig 1. Disposition of patients. (*) Two patients assigned to placebo treatment received at least one dose of motesanib. C/P, carboplatin/paclitaxel; QD, once daily.

Table 1. Baseline Demographics and Disease Characteristics*

Characteristic	Arm A, Motesanib + C/P (n = 541) No.	%	Arm B, Placebo + C/P (n = 549) No.	%
Age, years				
Median	60		60	
Range	23-87		21-84	
Men‡	334	62	336	61
ECOG performance status				
0	188	35	207	38
≥ 1	353	65	342	62
Past or present smoker	387	72	397	72
Race				
White	362	67	353	64
Asian§	139	26	148	27
Hispanic	28	5	38	7
Black	9	2	7	1
Other	3	< 1	3	< 1
Histology				
Adenocarcinoma	448	83	442	81
Bronchoalveolar carcinoma	14	3	15	3
Large-cell carcinoma	26	5	35	6
Undifferentiated	21	4	21	4
Other	32	6	36	7
Disease stage at study entry‡				
IIIB with pericardial/pleural effusion	73	13	79	14
IV/recurrent	468	87	470	86
Weight loss < 5% in previous 6 months†	397	73	407	74
Prior adjuvant chemotherapy‡	11	2	12	2

Abbreviations: C/P, carboplatin/paclitaxel; ECOG, Eastern Cooperative Oncology Group.
*All randomly assigned patients with nonsquamous histology.
‡Randomization stratification factors.
§Includes Japanese patients.

subset were similar: 5.6 months in arm A versus 5.4 months in arm B (HR, 0.78; 95% CI, 0.67 to 0.91; $P = .0016$; Fig 4B). *P* values for PFS and other secondary efficacy end points are exploratory because the study end point (OS) was not achieved.

Tumor Response

Most patients had measurable disease at baseline (Table 2). In exploratory analyses, ORR for all patients with nonsquamous histology (arm A, 40% *v* arm B, 26%) and for the adenocarcinoma subset (arm A, 39% *v* arm B, 25%) favored arm A. Likewise, in both the overall nonsquamous population (arm A, 80% *v* arm B, 74%) and the adenocarcinoma subset (arm A, 81% *v* arm B, 74%), more patients receiving motesanib than placebo had a decrease in the sum of longest diameter at any time after baseline. Duration of response was 5.8 months (95% CI, 5.3 to 6.5 months) in arm A and 5.0 months (95% CI, 4.4 to 5.6 months) in arm B.

Toxicity

Toxicity data are reported for all randomly assigned patients with nonsquamous histology. The incidence of grade 3 AEs was similar with both treatments; however, grade 4 and grade 5 AEs as well as serious grade ≥ 3 AEs occurred more frequently in arm A (Table 3). No specific events accounted for the imbalance in the incidence of grade 4 or 5 AEs with the exception of grade 4 neutropenia (12% of patients in arm A *v* 6% in arm B). Considering all AEs, there were a number of events that occurred at an increased incidence of ≥ 5% in arm A compared with placebo (Table 3). Particularly noteworthy were diarrhea, nausea, vomiting, and abdominal pain as well as hypertension, pneumonia, and gallbladder-related disorders (eg, cholecystitis, cholelithiasis, and gallbladder enlargement), some of which were also reported as serious grade ≥ 3 AEs.

The incidence of AEs typically associated with VEGF pathway inhibitors was higher in arm A with respect to hypertension (Table 3) and grade ≥ 3 arterial thromboembolic (2% *v* < 1% in arm B) and hemorrhagic events (3% *v* 1%). Specific hemorrhagic events were gastrointestinal hemorrhage (n = 1 *v* n = 0), pulmonary hemorrhage (n = 2 *v* n = 1), and hemoptysis (n = 3 *v* n = 1). Grade ≥ 3 venous thromboembolic events occurred in 4% of patients in each treatment arm.

The number of patients with AEs leading to motesanib/placebo discontinuation was higher in arm A (31%) than in arm B (15%). Fourteen percent of patients in arm A and 9% in arm B had fatal AEs while on study (ie, within 30 days of the last study treatment). Grade 5 AEs reported in four or more patients in either treatment arm were

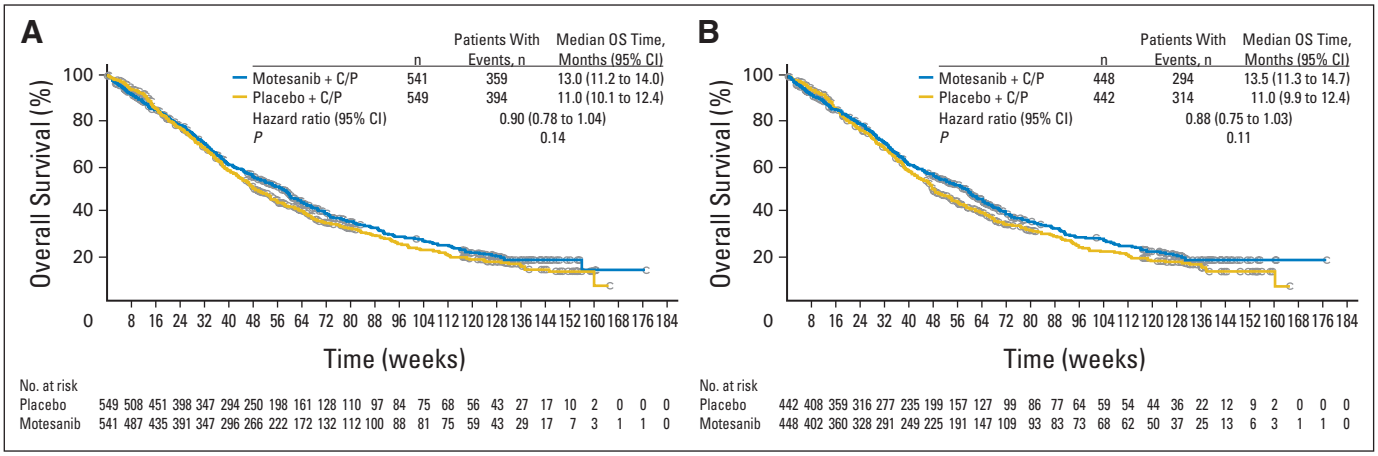

Fig 2. Overall survival (OS) time among patients who received motesanib 125 mg once daily plus carboplatin/paclitaxel (C/P) or placebo plus C/P in (A) all randomly assigned patients with nonsquamous histology and (B) the adenocarcinoma subset.

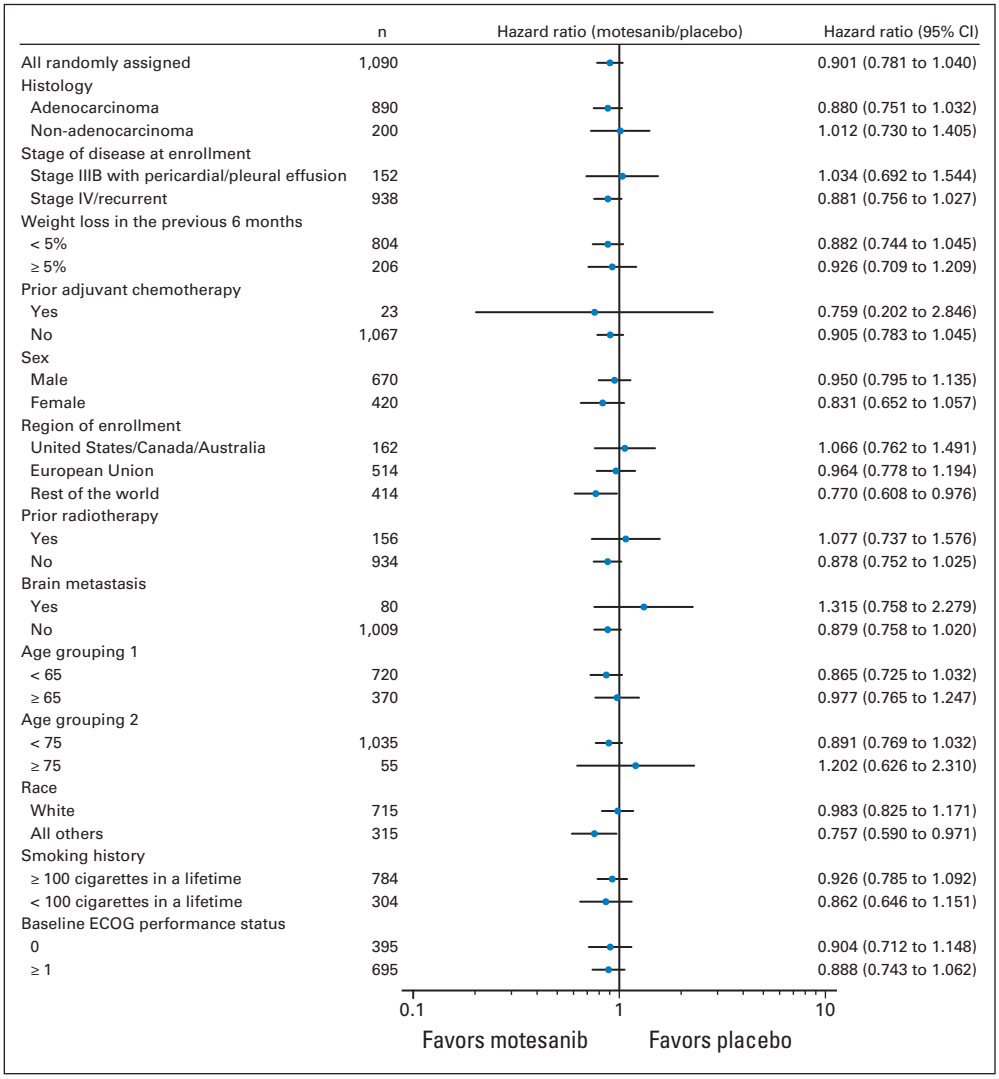

Fig 3. Overall survival time by patient subgroups for all randomly assigned patients with nonsquamous histology. European Union countries include Austria, Bulgaria, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Romania, Slovakia, Spain, and United Kingdom. ECOG, Eastern Cooperative Oncology Group.

pneumonia (n = 7 *v* n = 0), general physical health deterioration (n = 6 *v* n = 1), respiratory failure (n = 5 *v* n = 2), pulmonary embolism (n = 3 *v* n = 6), and cardiorespiratory arrest (n = 1 *v* n = 4).

Assessment of PLGF As a Biomarker

MONET1 confirmed the pharmacodynamic increase in PLGF in response to motesanib treatment that was reported previously[9,12,16,17] (data not shown). However, among patients in the motesanib arm who had evaluable PLGF samples at baseline (n = 356, 33%), there was no association between the log-transformed fold-change in PLGF from baseline to week 4 (continuous variable) and OS (unadjusted Cox model, HR, 0.98; 95% CI, 0.79 to 1.22; $P = .868$). There was no association between the prespecified ≥ 2.0-fold change in PLGF from baseline at week 4 and OS (HR, 0.88; 95% CI, 0.67 to 1.15, $P = .340$). Similarly, there was no association between a ≥ 2.0-fold change in PLGF and PFS or ORR.

DISCUSSION

In this large phase III study, motesanib plus carboplatin/paclitaxel did not significantly improve OS compared with placebo plus carboplatin/paclitaxel in the overall nonsquamous patient population or the subset of patients with adenocarcinoma. Although the study did not meet its primary end point, improvements in PFS and ORR in arm A suggest some antitumor activity of the combination in this setting. However, the study also showed that motesanib treatment was associated with increased toxicity, which may have affected efficacy. Specifically, the incidence of grade 4 and 5 AEs, serious grade ≥ 3 AEs, and AEs leading to discontinuation was higher with motesanib treatment. Gastrointestinal events, hypertension, pneumonia, cholecystitis, and other gallbladder-related disorders generally occurred more frequently in the motesanib arm, which is consistent with previous motesanib studies in advanced nonsquamous NSCLC.[11,18] Cholecystitis in particular is a motesanib-specific AE that had emerged in earlier monotherapy and chemotherapy combination studies.[8,9,11,18-20] Most of these AEs are likely the result of motesanib's actions on angiogenic signaling pathways (motesanib potently inhibits VEGFR1, -2, and -3; Kit; and PDGFR[7]). Toxicity in the motesanib arm appeared to have contributed to treatment discontinuation and may also have resulted in noncompliance with treatment. The study initially permitted enrollment of both nonsquamous and squamous NSCLC; however, the protocol was later amended to

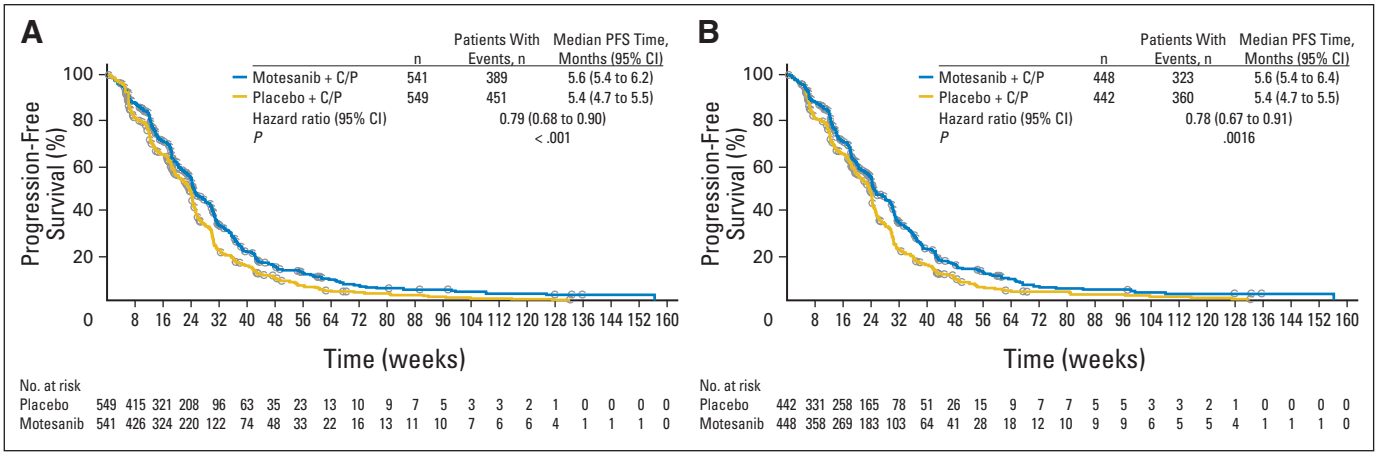

Fig 4. Progression-free survival time among patients who received motesanib 125 mg once daily plus carboplatin/paclitaxel (C/P) or placebo plus C/P in (A) all randomly assigned patients with nonsquamous histology and (B) the adenocarcinoma subset.

exclude patients with squamous histology because of an increased risk of death and hemoptysis. This finding was consistent with the greater risk of hemoptysis reported for patients with squamous NSCLC who received bevacizumab,[21] but not with results from the Evaluation of Sorafenib, Carboplatin, and Paclitaxel Efficacy in NSCLC (ESCAPE) study, which showed no increased risk of fatal bleeding events with sorafenib treatment among patients with squamous histology.[22]

A number of phase III studies have assessed VEGF pathway inhibitors as first-line therapy for advanced NSCLC. At present, only one has demonstrated an OS benefit.[1] Sorafenib plus chemotherapy did not achieve OS improvements in either the ESCAPE[22] (sorafenib plus carboplatin/paclitaxel in squamous or nonsquamous NSCLC) or NEXUS[23] (NSCLC Research Experience Utilizing Sorafenib; sorafenib plus cisplatin/gemcitabine in nonsquamous NSCLC) studies, although PFS was improved in NEXUS. Lastly, in BR24, a phase II/III study of carboplatin/paclitaxel with or without cediranib in squamous or nonsquamous NSCLC, PFS and ORR were improved over placebo plus carboplatin/paclitaxel; however, the study was halted because cediranib at 30 mg/d was associated with increased incidences of severe hypertension, gastrointestinal toxicity, and

Table 2. Tumor Response per RECIST*

	Nonsquamous Analysis Set				Adenocarcinoma Subanalysis Set			
	Arm A, Motesanib + C/P (n = 541)		Arm B, Placebo + C/P (n = 549)		Arm A, Motesanib + C/P (n = 448)		Arm B, Placebo + C/P (n = 442)	
Response	No.	%	No.	%	No.	%	No.	%
Patients with measurable disease at baseline	523	97	527	96	433	97	422	95
Response assessment								
Confirmed CR	5	< 1	2	< 1	5	1	1	< 1
Confirmed PR	204	39	133	25	166	38	105	25
SD†	207	40	265	50	182	42	214	51
PD	35	7	80	15	26	6	64	15
Unevaluable‡	5	< 1	2	< 1	5	1	2	< 1
Not done§	67	13	45	9	49	11	36	9
Confirmed objective response (CR or PR)	209	40	135	26	171	39	106	25
Difference, %		14.3				14.4		
95% CI		8.7 to 20.0				8.2 to 20.6		
P‖		< .001				< .001		
Responders with measurable disease at baseline	209	39	135	25	171	38	106	24
Duration of response, months	5.8		5.0		5.9		5.5	
95% CI	5.3 to 6.5		4.4 to 5.6		5.5 to 6.9		4.4 to 5.7	

Abbreviations: C/P, carboplatin/paclitaxel; CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

*Assessed by investigators per RECIST version 1.0. The nonsquamous analysis set included all patients randomly assigned who had nonsquamous histology. The adenocarcinoma analysis set included all patients randomly assigned who had adenocarcinoma histology. The denominator for all response categories was the number of patients with measurable disease at baseline.

†Patients with an assessment of PR or CR not confirmed at least 4 weeks later were classified as having SD.

‡Patients with an assessment of CR, PR, or SD before the first scheduled assessment of response without an additional assessment of response.

§Patients for whom imaging was not performed at the scheduled assessment of response.

‖From Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

Table 3. Adverse Events

AE	Arm A, Motesanib + C/P (n = 533) No.	%	Arm B, Placebo + C/P (n = 539) No.	%
Patients with any AE	512	96	520	96
Grade 3	201	38	192	36
Grade 4	113	21	77	14
Grade 5	74	14	50	9
AEs with a ≥ 5% difference in incidence between arms				
Diarrhea	255	48	118	22
Nausea	222	42	176	33
Decreased appetite	186	35	147	27
Vomiting	178	33	142	26
Fatigue	177	33	151	28
Neutropenia	149	28	110	20
Hypertension	139	26	35	6
Thrombocytopenia	112	21	83	15
Rash	97	18	57	11
Weight decreased	93	17	46	9
Abdominal pain	90	17	30	6
Headache	82	15	49	9
Stomatitis	59	11	26	5
Proteinuria	47	9	16	3
Gallbladder-related disorder*	44	8	2	< 1
Patients with serious AEs	261	49	184	34
Serious grade ≥ 3 AEs†				
Neutropenia	28	5	12	2
Diarrhea	25	5	4	< 1
Febrile neutropenia	23	4	15	3
Pneumonia	20	4	7	1
Dehydration	19	4	4	< 1
Non–small-cell lung cancer‡	16	3	12	2
Thrombocytopenia	14	3	6	1
Pulmonary embolism	12	2	17	3
Anemia	12	2	11	2
Dyspnea	11	2	20	4
Vomiting	11	2	7	1
General physical health deterioration	11	2	4	< 1
Cholecystitis	11	2	0	0

NOTE. AEs are reported for all patients with nonsquamous histology who received ≥ 1 dose of motesanib or placebo and include events occurring during treatment and within 30 days of the last administration of study treatment.

Abbreviations: AE, adverse event; C/P, carboplatin/paclitaxel.

*Includes cholecystitis, acute and chronic cholecystitis, cholelithiasis; gallbladder enlargement, edema, and perforation; hydrocholecystis (the difference in incidence between arms for individual AEs was < 5%).

†In ≥ 2% of patients in either treatment arm.

‡Patients with non–small-cell lung cancer reported as an AE by investigators.

febrile neutropenia and was not considered tolerable.[24] Furthermore, two randomized studies evaluating VEGF pathway inhibitors as second-line therapy in advanced NSCLC failed to meet their primary end points.[25,26] The results from MONET1 add to the growing body of evidence suggesting that VEGF pathway inhibitors in combination with chemotherapy do not provide a significant clinical benefit to unselected patients with (nonsquamous) NSCLC. Additional studies do not seem to be warranted unless better patient selection using biomarkers, for example, can be achieved. Despite ongoing efforts,[27] such biomarkers have remained elusive. MONET1 is the first large phase III study to prospectively test a biomarker hypothesis for an antiangiogenic therapy in NSCLC. Data from the preceding phase II study of carboplatin/paclitaxel plus motesanib or bevacizumab suggested that increased PLGF might be a marker of therapeutic response to motesanib treatment.[12] This hypothesis was supported by similar findings of associations between fold-change in PLGF and outcomes in patients with advanced thyroid cancer[17] and human epidermal growth factor receptor 2–negative metastatic breast cancer[12] receiving motesanib. However, the data could not be confirmed in MONET1; there was no association between changes in PLGF and OS in the motesanib arm.

Previous studies suggested that NSCLC tumor histology influences response to certain chemotherapy regimens[28] and targeted agents (including VEGF pathway inhibitors).[6,29] A retrospective analysis of the E4599 study reported a 4-month improvement in OS with the addition of bevacizumab to carboplatin/paclitaxel among patients with adenocarcinoma histology.[6] On the basis of those data, we conducted a prospectively defined analysis of efficacy in the subset of patients with adenocarcinoma histology. Although a statistically significant improvement in OS was not achieved, it is noteworthy that in prespecified subgroup analyses, the HR for patients with adenocarcinoma histology was 0.880 versus 1.012 for those with other nonsquamous histologies.

Prespecified subgroup analyses also indicated differences in OS by ethnicity and geographic location. The subanalyses data suggest that a highly selected patient population might have a greater likelihood to benefit. Specifically, results from the ethnicity/regional subanalysis indicate that Asian patients (one fourth of the enrolled patient population) may achieve better clinical outcome than non-Asian patients (data not shown), which may warrant a separate study in the future.

In summary, treatment with motesanib plus carboplatin/paclitaxel in this phase III study did not significantly improve OS and was associated with a higher incidence of AEs compared with placebo plus carboplatin/paclitaxel in patients with advanced nonsquamous NSCLC and in the subset of patients with adenocarcinoma histology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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