Motesanib Plus Carboplatin/Paclitaxel in Patients With Advanced Squamous Non–Small-Cell Lung Cancer

Results From the Randomized Controlled MONET1 Study

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Introduction: The phase 3 MONET1 study evaluated motesanib (a small-molecule inhibitor of vascular endothelial growth factor receptors) plus carboplatin/paclitaxel versus placebo plus carboplatin/paclitaxel as first-line therapy for advanced non–small-cell lung cancer (NSCLC). Treatment and enrollment of patients with squamous histology were permanently discontinued following higher early mortality and gross hemoptysis in those with squamous NSCLC who received motesanib. Enrollment of patients with nonsquamous histology was temporarily halted, but resumed following a protocol amendment (Scagliotti et al. *J Clin Oncol*. 2012;30:2829–2836). Herein, we report data from the squamous cohort.

Methods: Patients with stage IIIB/IV or recurrent squamous NSCLC (without prior systemic therapy for advanced disease) received up to six 3-week cycles of chemotherapy (carboplatin, area under the curve 6 mg/mL•min/paclitaxel, 200 mg/m^2) and were randomized 1:1 to receive motesanib 125 mg (Arm A) or placebo (Arm B) once daily. The primary end point was overall survival.

Results: Three-hundred and sixty patients with squamous NSCLC were randomized (Arm A, n = 182; Arm B, n = 178) between July 2007 and November 2008. Twenty-three patients (13%) in Arm A and 10 (6%) in Arm B had fatal adverse events within the first 60 days of treatment. Among these, six patients in Arm A, but none in Arm B, had fatal bleeding events. At final analysis, serious adverse events had occurred in 47% of patients in Arm A and 29% of patients in Arm B. Median overall survival was similar in Arms A and B (11.1 versus 10.7 months).

Conclusions: Motesanib plus carboplatin/paclitaxel had unacceptable toxicity compared with carboplatin/paclitaxel alone in patients with advanced squamous NSCLC.

Key Words: Squamous histology, NSCLC, Motesanib, Carboplatin, Paclitaxel

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For patients with squamous cell carcinoma of the lung, two-drug chemotherapy regimens (including carboplatin/paclitaxel [C/P]) are a cornerstone of current treatment options.[1,2] However, outcomes associated with conventional therapies remain poor,[3] underlining the clear need for alternative approaches to treatment in this patient population. Some studies have evaluated combinations of targeted therapies plus standard-of-care chemotherapy in this setting. At present only one study that enrolled patients with squamous histology as part of a larger study in advanced non–small-cell lung cancer (NSCLC; 377 of 1125 patients; 34%) has demonstrated an overall survival (OS) benefit.[4] That study (FLEX) investigated the addition of cetuximab to cisplatin/vinorelbine and showed an OS improvement of 1.2 months compared with cisplatin/vinorelbine alone in an open-label, randomized phase 3 trial in patients with NSCLC.[4]

Angiogenesis is required for the development and progression of solid tumors, including NSCLC.[5] Signaling through the vascular endothelial growth factor (VEGF) pathway has been shown to play a central role in the angiogenic

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processes that contribute to the development, growth, and metastasis of NSCLC.[6] To date, bevacizumab, a monoclonal anti-VEGF antibody, is the only angiogenesis inhibitor that has been shown to improve OS[7] and progression-free survival (PFS)[7–9] as first-line therapy in combination with chemotherapy in patients with nonsquamous NSCLC. Bevacizumab is contraindicated for patients with squamous NSCLC because the combination of bevacizumab plus C/P was associated with a high incidence of severe hemorrhage among patients with squamous histology in a phase 2 study.[10] Tyrosine kinase inhibitors of the VEGF pathway, such as vandetanib,[11] cediranib,[12] and sorafenib,[13,14] that have been evaluated as first-line treatment in patients with NSCLC of all or selected lung cancer histologies have failed to show a survival benefit. Those studies that also enrolled and treated patients with squamous NSCLC (between 18% and 24% of the total enrolled patient populations with NSCLC) did not provide sufficient evidence in support of a positive risk-benefit profile.[11–13]

Motesanib is an oral, small-molecule inhibitor of VEGF receptors 1, 2, and 3; Kit; and platelet-derived growth factor receptor (PDGFR)[15] that has demonstrated antitumor activity in histologically diverse xenograft models of lung cancer[16] and in patients with a variety of solid tumors.[17–20] In the randomized phase 3 MONET1 study, which enrolled patients between July 5, 2007, and March 18, 2010, motesanib plus C/P, compared with placebo plus C/P, did not significantly improve OS in patients with nonsquamous NSCLC ($N = 1090$).[21] Initially, MONET1 enrolled patients with both nonsquamous and squamous histology. After higher rates of early mortality and gross hemoptysis emerged in the MONET1 study among patients with squamous histology randomized to motesanib, the study was temporarily stopped and subsequently amended to allow continued enrollment of patients with nonsquamous NSCLC only.[21] Before the study stop, a total of 354 patients with squamous NSCLC histology had received at least one dose of motesanib ($n = 180$) or placebo ($n = 174$). Herein, we report detailed early and overall toxicity data along with clinical outcomes in this patient cohort, one of the largest to date with the NSCLC squamous cell histologic subtype that has been recruited to a first-line randomized trial.

METHODS

Eligibility

All patients provided written informed consent and the study protocol was approved by an independent ethics committee or institutional review board at each study site. Eligible patients were at least 18 years of age and had histologically confirmed unresectable stage IIIB with pericardial/pleural effusion or stage IV/recurrent NSCLC and measurable or nonmeasurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.[22] Key exclusion criteria were life expectancy less than 3 months; an Eastern Cooperative Oncology Group performance status greater than or equal to 2; untreated or symptomatic central nervous system metastases; prior chemotherapy, including adjuvant chemotherapy within 52 weeks of randomization; prior targeted therapy; central or peripheral radiation within 28 or 14 days, respectively; arterial or venous thrombosis within 12 months; pulmonary hemorrhage or gross hemoptysis within 6 months of randomization; bleeding diathesis or bleeding within 14 days; uncontrolled hypertension (defined as resting blood pressure >150/90 mmHg; antihypertensive medications were allowed if the patient was stable on their current dose at the time of randomization); and inadequate renal cardiac, hepatic, or hematologic function.

Study Design and Treatments

This phase 3, randomized, placebo-controlled, double-blind study was conducted at 198 centers in 32 countries.[21] Using a computerized interactive voice response system, patients were randomized 1:1 to receive either motesanib 125 mg once daily (Arm A) or placebo (Arm B). All patients also received chemotherapy (carboplatin, [area under the curve 6 mg/mL·min]/paclitaxel, 200 mg/m^2) beginning on day 1 of each 3-week cycle up to a maximum of six cycles. Randomization was stratified by the following factors: histology (nonsquamous versus squamous), disease stage (IIIB versus IV/recurrent), weight loss in the 6 months before randomization (<5% versus ≥5%), sex (male versus female), and prior adjuvant chemotherapy (yes versus no).

Treatment was planned to continue until patients experienced disease progression, had unacceptable toxicity, or withdrew consent, for a maximum of 36 months. Modifications of doses and treatment discontinuations followed the rules reported previously.[21] Specifically, if grade ≥2 bleeding or hemoptysis occurred, motesanib/placebo was permanently discontinued. For other grade 3/4 treatment-related toxicities, motesanib/placebo was withheld until the toxicity resolved to grade ≤1 or baseline. If the toxicity resolved, treatment could be resumed with a 25-mg dose reduction; all dose reductions were permanent. Motesanib/placebo was discontinued permanently if more than two dose reductions were required, grade 3/4 toxicity recurred after a dose delay and/or reduction, or grade 3/4 toxicity persisted for more than 3 weeks.

Study Protocol Amendment

In November 2008, the study's independent data monitoring committee reviewed data from the first 600 patients enrolled, including 223 patients with squamous histology. The committee recommended that enrollment of all patients be stopped and that treatment of patients with squamous NSCLC be discontinued because the data indicated a higher early mortality and a higher event rate of gross hemoptysis in those patients with squamous histology who received motesanib compared with placebo.[21] Patients with squamous NSCLC immediately discontinued blinded treatment with motesanib and placebo, but continued to receive up to six cycles of C/P per protocol. Patients also continued their study visits (every 3 weeks) and radiological imaging (as described below) to assess disease status. Enrollment of patients with nonsquamous NSCLC was subsequently reinstated.[21]

Study End Points

The primary end point was OS (time from randomization to death). Secondary endpoints included PFS (time from randomization to disease progression per RECIST, or death from any cause); objective response rate (ORR) per RECIST,[22] and incidence of treatment-emergent adverse events (AEs).

Assessments

Tumor assessments were performed by computed tomography/magnetic resonance imaging every 6 ± 1 weeks. Tumor response was evaluated by investigators according to RECIST version 1.0.[22] Objective responses were required to be confirmed ≥4 weeks after the initial assessment of response.

AEs occurring during the study (study day 1–30 days after the last dose) were recorded and classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[23] Serious AEs were defined as AEs that were fatal, life threatening, required hospitalization or prolongation of hospitalization, or resulted in significant disability/incapacity or other medical hazard.

Statistical Analysis

The MONET1 study was originally designed to enroll approximately 1240 patients (all histologies). All analyses of outcomes in the squamous patient population are descriptive only and not intended to allow statistical inference. The squamous analysis set included all patients randomized under the squamous stratification or with a squamous component (squamous, adenosquamous, or mixed histology) noted on the case report form at baseline. Cox proportional hazard models were used to estimate hazard ratios (HRs) for the treatment effect of motesanib versus placebo on OS and PFS.[24] Comparisons of OS and PFS between Arms A and B were performed using log-rank tests stratified by the randomization stratification factors. Differences in ORR between Arms A and B were evaluated using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. Analyses of OS and PFS included all randomized patients with squamous histology per the intent-to-treat principle. The analysis of ORR included all patients with measurable disease at baseline. Interim and final safety analyses included all randomized patients with squamous histology who received at least one dose of motesanib or placebo.

RESULTS

Demographics and Baseline Characteristics

Between July 5, 2007, and November 14, 2008, 360 patients with squamous histology were randomized to receive motesanib (n = 182; Arm A) or placebo (n = 178; Arm B) (Fig. 1). Six patients did not receive motesanib (n = 2) or placebo (n = 4). Demographic and clinical characteristics were balanced across the two treatment arms. The majority of patients had Eastern Cooperative Oncology Group performance status of 1, stage IV/recurrent disease, and weight loss less than 5% in the 6 months before randomization (Table 1).

Treatment

The median daily doses of motesanib or placebo administered were 125 mg in both treatment arms. Patients received motesanib for a median of 67 days (range, 1−323 days) and placebo for 93 days (range, 2−375 days). Patients in Arm A received a median of four cycles (range, one to six cycles) of carboplatin; patients in Arm B received a median of six cycles (range, one to six cycles). Similarly, patients in Arm A received a median of four cycles (range, one to six cycles) of paclitaxel, whereas patients in Arm B received a median of six cycles (range, one to six cycles). In Arm A, 39% of patients completed all 6 cycles of chemotherapy treatment; in Arm B, 52% of patients completed treatment. Consistent with the data monitoring committee's recommendation (see Methods—Study Amendment), all patients with squamous histology had discontinued motesanib/placebo at the time of this analysis. The number of patients who discontinued treatment because of the study amendment (i.e., administrative decision) was 74 (41%) in Arm A and 72 (40%) in Arm B.

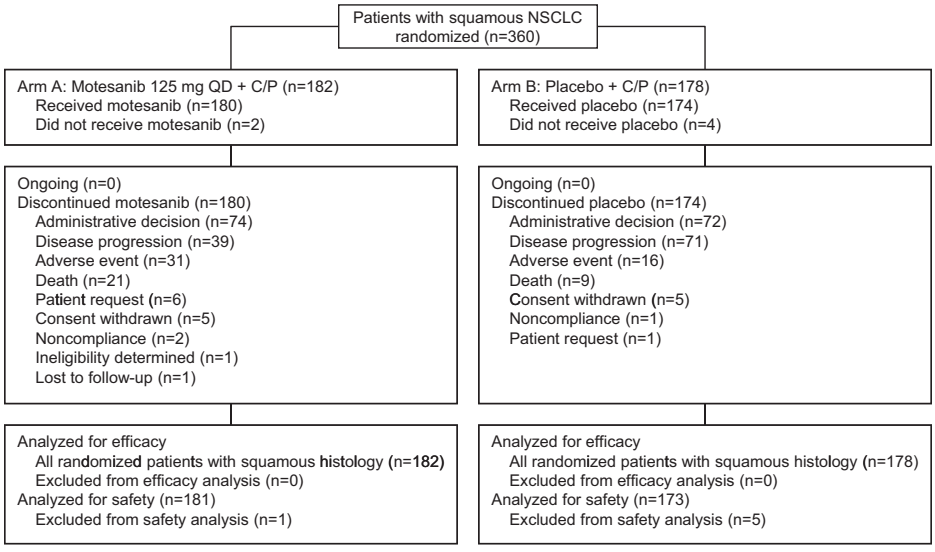

FIGURE 1. Disposition of patients. "Administrative decision" refers to the study amendment (immediate discontinuation of blinded motesanib/placebo treatment of patients with squamous NSCLC histology). One patient in the placebo arm received at least one dose of motesanib and, therefore, was included in the safety analysis of the motesanib and not the placebo arm. C/P, carboplatin/paclitaxel; NSCLC, non–small-cell lung cancer; QD, once daily.

TABLE 1. Baseline Demographics and Disease Characteristics[a]

	Arm A Motesanib + C/P (*n* = 182)	Arm B Placebo + C/P (*n* = 178)
Median age, years (range)	62.0 (31–79)	59.5 (32–81)
Men,[b] *n* (%)	145 (80)	150 (84)
ECOG performance status, *n* (%)		
0	64 (35)	66 (37)
1	118 (65)	111 (62)
Missing	0 (0)	1 (<1)
Past or present smoker, *n* (%)	153 (84)	159 (89)
Race, *n* (%)		
White	132 (73)	132 (74)
Asian[c]	39 (21)	29 (16)
Hispanic	9 (5)	11 (6)
Black	1 (<1)	5 (3)
Other	1 (<1)	1 (<1)
Disease stage at study entry,[b] *n* (%)		
Stage IIIB with pericardial/pleural effusion	28 (15)	25 (14)
Stage IV/recurrent	154 (85)	153 (86)
Weight loss <5% in previous 6 months,[b] *n* (%)	139 (76)	136 (76)
Brain metastases,[d] *n* (%)		
Yes	9 (5)	9 (5)
No	172 (95)	169 (95)
No information available	1 (<1)	0 (0)
Prior adjuvant chemotherapy,[b] *n* (%)	2 (1)	3 (2)
Histology, *n* (%)		
Adenocarcinoma[e]	0 (0)	2 (1)
Squamous cell carcinoma	174 (96)	173 (97)
Undifferentiated	1 (<1)	0 (0)
Other[f]	7 (4)	3 (2)

C/P, carboplatin/paclitaxel; ECOG, Eastern Cooperative Oncology Group.
[a]For all randomized patients with squamous histology.
[b]Randomization stratification factors.
[c]Includes Japanese patients.
[d]All patients with brain metastases had received prior radiotherapy, with the exception of one patient in the motesanib arm for whom no radiotherapy was reported.
[e]Adenocarcinoma with squamous cell components and adenosquamous/adenocarcinoma, respectively.
[f]Includes adenosquamous (*n* = 6), non-small cell (*n* = 2), and mixed histology (adenocarcinoma with squamous; *n* = 2).

Study discontinuation as a result of AEs or death was higher in Arm A than B (Fig. 1). Median follow-up times were 43.5 days (range, 1–160 days) in Arm A and 42.5 days (1–163 days) in Arm B.

Early Toxicity

Twenty-three patients (13%) in Arm A and 10 patients (6%) in Arm B had fatal AEs within 60 days of initiating treatment. The most notable AEs with early onset and fatal outcome were bleeding events, which occurred only in patients who received motesanib: five patients in Arm A had grade 5 pulmonary hemorrhage and one patient had grade 5 hemoptysis (no grade 5 bleeding events among patients in Arm B). Fatal pulmonary hemorrhage in the motesanib arm developed as early as 30 days within treatment start (*n* = 4 patients versus *n* = 0 in the placebo arm). Within 60 days of initiating treatment, five patients in Arm A had grade 5 cardiac toxicity (cardiorespiratory arrest, cardiopulmonary failure, circulatory collapse, myocardial infarction, and myocardial ischemia; *n* = 1 each) compared with only one patient in Arm B (congestive cardiac failure). Fatal AEs that occurred with both motesanib and placebo treatment were grade 5 respiratory failure (Arms A/B, *n* = 2/1), acute respiratory failure (*n* = 1/1), multiorgan failure (*n* = 1/1), and NSCLC (i.e., death due to disease progression; *n* = 1/1). Two patients in Arm B had pneumonia (no events in Arm A).

Serious AEs that emerged during the first 6 months of treatment also occurred more frequently in patients in Arm A than in patients randomized to Arm B (46% versus 28%; Table 2). Specific AEs accounting for this difference in incidence between treatment arms included diarrhea (7% of patients in Arm A versus <1% in Arm B), dehydration (5% versus 2%, respectively), and pulmonary hemorrhage (3% versus 0%).

Toxicity Throughout the Study

The incidence of grade 3 AEs, grade 5 AEs, and serious AEs throughout the study was also greater among patients in Arm A than Arm B; the incidence of grade 4 AEs was similar across arms (Table 3). Twenty percent of patients in Arm A had AEs leading to discontinuation, compared with 10% in Arm B. AEs occurring with an increased incidence of at least 5% in Arm A compared with Arm B included diarrhea, alopecia, nausea, and vomiting (Table 3). Hypertension occurred in 26% of patients in Arm A and 9% of patients in Arm B.

Specific serious grade ≥3 hemorrhagic events included pulmonary hemorrhage (Arm A, *n* = 5 versus Arm B, *n* = 0) and hemoptysis (*n* = 2 versus *n* = 1, respectively), most of which occurred in the early treatment phase (see above); gastrointestinal hemorrhage (*n* = 1 versus *n* = 0), and gastric ulcer hemorrhage (*n* = 1 versus *n* = 0). With the exception of one event of hemoptysis in Arm A (grade 4) and the gastric ulcer hemorrhage (grade 3, Arm A), all serious hemorrhagic events on study were grade 5. Serious grade ≥3 gallbladder disorders (all grade 3) occurred only in patients in Arm A (cholecystitis, *n* = 2; acute cholecystitis, gallbladder enlargement, and gallbladder disorder, *n* = 1 each). The incidence of serious grade ≥3 thromboembolic events (all grade 3) was similar in Arms A and B (pulmonary embolism, *n* = 0 and *n* = 1; arterial thrombosis, *n* = 0 and *n* = 1; deep vein thrombosis, *n* = 1 and *n* = 0).

Over the course of the study (i.e., within 30 days of their last dose), 37 patients (20%) in Arm A and 21 patients (12%) in Arm B had grade 5 AEs. Those that accounted for notable differences between treatment arms included NSCLC (Arm A, *n* = 4; Arm B, *n* = 5), pulmonary hemorrhage (*n* = 5 versus *n* = 0, respectively), pneumonia (*n* = 0 versus *n* = 3), cardiorespiratory arrest (*n* = 2 versus *n* = 1), respiratory failure (*n* = 2 versus *n* = 1), and cardiopulmonary failure (*n* = 2 versus *n* = 0). Additional grade 5 cardiac toxicities reported

TABLE 2. Serious Adverse Events Occurring Within 6 Months of Treatment Initiation[a]

	Arm A Motesanib + C/P (*n* = 181)	Arm B Placebo + C/P (*n* = 173)
Patients with any serious adverse event, *n* (%)	84 (46)	48 (28)
Any serious adverse event, *n* (%)[b]		
Diarrhea	12 (7)	1 (<1)
Dehydration	9 (5)	3 (2)
Dyspnea	8 (4)	6 (3)
Neutropenia	8 (4)	5 (3)
Anemia	7 (4)	6 (3)
Pneumonia	6 (3)	9 (5)
Vomiting	6 (3)	3 (2)
Febrile neutropenia	5 (3)	1 (<1)
Hemoptysis	5 (3)	1 (<1)
Thrombocytopenia	5 (3)	1 (<1)
Pulmonary hemorrhage	5 (3)	0 (0)
Asthenia	4 (2)	1 (<1)
Fatigue	4 (2)	1 (<1)
Nausea	4 (2)	1 (<1)
Pleural effusion	4 (2)	0 (0)
Hypotension	3 (2)	2 (1)
Abdominal pain	3 (2)	1 (<1)
Decreased appetite	3 (2)	0 (0)
Sepsis	3 (2)	0 (0)
Pyrexia	1 (<1)	3 (2)

C/P, carboplatin/paclitaxel.
[a]Serious adverse events are reported for all patients with squamous 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.
[b]In ≥2% of patients in either treatment arm.

included cardiac arrest (*n* = 1 versus *n* = 0), myocardial infarction (*n* = 1 versus *n* = 0), myocardial ischemia (*n* = 1 versus *n* = 0), and congestive cardiac failure (*n* = 0 versus *n* = 1).

Efficacy Results

At the time of this analysis, 145 patients in Arm A and 150 patients in Arm B had died (total, 82%). Median overall OS time in Arm A was 11.1 months (95% confidence interval [CI], 9.0–12.8 months) compared with 10.7 months (95% CI, 9.4–12.1 months) in Arm B (HR, 0.89; 95% CI, 0.71–1.12; $p = 0.3306$; Fig. 2A). In Arm A, median 1-year and 2-year survival rates were 46% and 21%, respectively. In Arm B, median 1-year and 2-year survival rates were 44% and 12%, respectively. Similarly, 114 patients in Arm A and 121 patients in Arm B had had PFS events at the time of this analysis. Median PFS times were 4.9 months (95% CI, 4.2–5.6 months) and 5.1 months (95% CI, 4.4–5.6 months) in Arms A and B, respectively (HR, 0.85; 95% CI, 0.65–1.11; $p = 0.2294$; Fig. 2B).

Nearly all patients had measurable disease at baseline (Table 4). The ORR in Arm A was 38% compared with 35% in Arm B (difference, 2.6%: 95% CI, −7.4 to 12.6; $p = 0.7362$). Among patients with a confirmed objective response, the duration of response was 7.2 months (95% CI, 4.8–9.1 months) for patients in Arm A versus 4.4 months (95% CI, 4.2–5.6 months) for patients in Arm B.

TABLE 3. Adverse Events Throughout the Study[a]

	Arm A Motesanib + C/P (*n* = 181)	Arm B Placebo + C/P (*n* = 173)
Patients with any adverse event, *n* (%)	172 (95)	157 (91)
Worst grade 3	59 (33)	46 (27)
Worst grade 4	18 (10)	15 (9)
Worst grade 5	37 (20)	21 (12)
Adverse events with ≥5% difference in incidence between arms, *n* (%)		
Diarrhea	69 (38)	28 (16)
Alopecia	62 (34)	70 (40)
Nausea	50 (28)	37 (21)
Hypertension	47 (26)	15 (9)
Vomiting	39 (22)	30 (17)
Decreased appetite	40 (22)	25 (14)
Anemia	33 (18)	43 (25)
Weight decreased	31 (17)	13 (8)
Thrombocytopenia	27 (15)	14 (8)
Headache	23 (13)	11 (6)
Abdominal pain	20 (11)	9 (5)
Arthralgia	18 (10)	30 (17)
Dehydration	17 (9)	6 (3)
Depression	12 (7)	4 (2)
Chest pain	11 (6)	24 (14)
Patients with serious adverse events, *n* (%)	85 (47)	50 (29)
Serious grade ≥3 adverse events in ≥2% of patients in either treatment arm	81 (45)	46 (27)
Diarrhea	9 (5)	0 (0)
Neutropenia	8 (4)	5 (3)
Dyspnea	7 (4)	7 (4)
Dehydration	7 (4)	2 (1)
Pneumonia	6 (3)	7 (4)
Pulmonary hemorrhage	5 (3)	0 (0)
Non–small-cell lung cancer[b]	5 (3)	4 (2)
Anemia	4 (2)	4 (2)
Vomiting	4 (2)	2 (1)
Febrile neutropenia	4 (2)	1 (<1)
Pleural effusion	4 (2)	0 (0)
Abdominal pain	3 (2)	1 (<1)
Nausea	3 (2)	1 (<1)
Fatigue	3 (2)	0 (0)
Decreased appetite	3 (2)	0 (0)
Sepsis	3 (2)	0 (0)
Thrombocytopenia	4 (2)	1 (<1)

AE, adverse event; C/P, carboplatin/paclitaxel.
[a]AEs are reported for all patients with squamous 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.
[b]Patients with non–small-cell lung cancer reported as an adverse event by investigators.

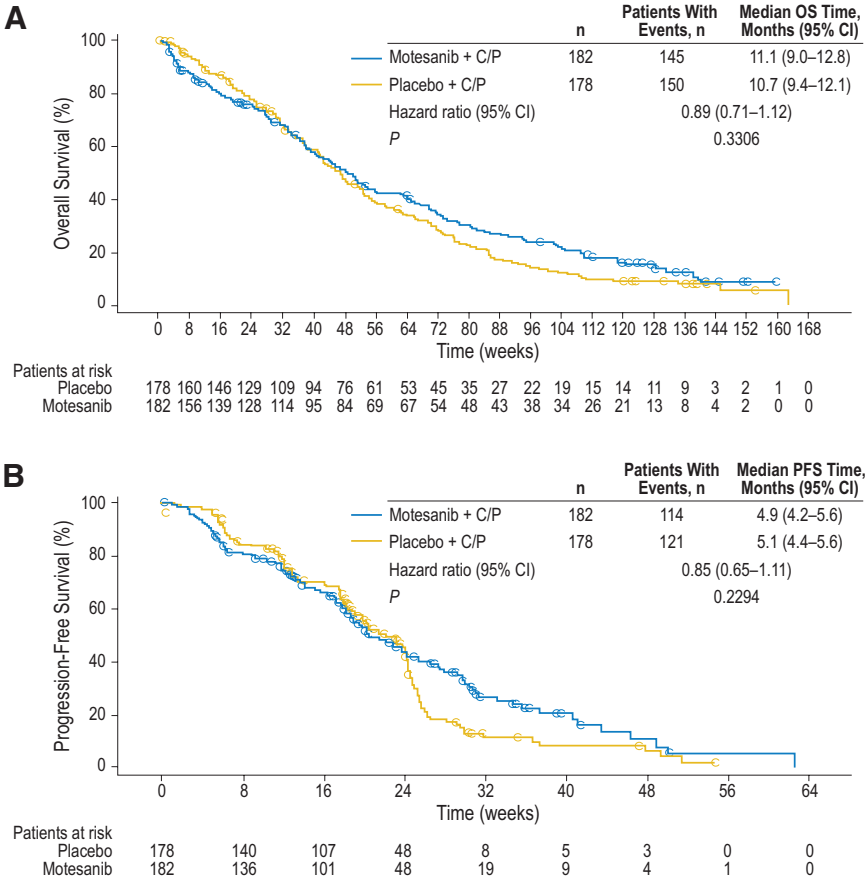

FIGURE 2. Overall survival time (*A*) and progression-free survival time (*B*) among patients who received motesanib 125 mg once daily plus carboplatin/paclitaxel or placebo plus carboplatin/paclitaxel in all randomized patients with squamous histology.

DISCUSSION

Although the initial objective of the MONET1 study—to evaluate motesanib in combination with C/P in patients with squamous and nonsquamous NSCLC histology—was not achieved, the study has provided one of the largest data sets of patients with squamous NSCLC treated with a VEGF receptor inhibitor. The results show early onset of increased risk of toxicity, particularly in the incidence of fatal AEs, among patients with squamous histology who received motesanib, with more than twice as many deaths in the motesanib arm (13%) than in the placebo arm (6%) during the first 60 days of treatment. The increased risk of early mortality appeared to be largely driven by hemorrhagic events: six patients in Arm A had grade 5 pulmonary hemorrhage or hemoptysis within 60 days of initiating treatment (no events occurred in Arm B), and four patients in Arm A developed grade 5 pulmonary hemorrhage within 30 days of initiating treatment. It appears that these toxicities contribute to the early divergence between the OS and PFS curves for Arms A and B (Fig. 2). Overall, fatal cardiac toxicities were reported more frequently in the motesanib arm. The overall incidences of grade ≥3 AEs, fatal AEs, serious AEs, and AEs leading to treatment discontinuation were also higher with motesanib compared with placebo. AEs accounting for these differences included hemorrhagic events, hypertension, gastrointestinal events, and gallbladder-related disorders (but not thromboembolic events), all of which have been reported in previous studies investigating motesanib as a monotherapy and in combination with chemotherapy.[17,19,20,25–30] Overall, the toxicity profile was consistent with earlier reports. Among patients who received placebo, the incidence of AEs was broadly consistent with toxicity anticipated for patients receiving C/P chemotherapy and with toxicity reported for placebo-treated patients in the MONET1 nonsquamous cohort.[3,4,31]

Increased risk of bleeding has been reported in some—but not all—studies evaluating VEGF pathway inhibitors as first-line therapy for advanced NSCLC in patient populations that included squamous histology. In a phase 2 study, four of 13 patients with squamous NSCLC and two of 54 patients with nonsquamous NSCLC who received bevacizumab plus C/P had severe life-threatening hemorrhagic events (none occurred in patients who received C/P alone).[10] The onset was both early (≤60 days) and late (≥180 days) during treatment. The specific onset of bleeding in patients with squamous NSCLC was not reported. In the phase 2/3 BR.24 study of cediranib or placebo plus C/P, the incidence of grade ≥3 bleeding events (3% versus 1%, respectively) and hemoptysis (2% versus 0%) were greater in patients receiving cediranib.[12] However, the tumor histology of these patients was not reported. In contrast, in the ESCAPE study, which evaluated sorafenib with or without C/P, sorafenib treatment was not associated with an increased risk of bleeding.[13] Although the incidence of fatal bleeding events was greater among patients with squamous compared with nonsquamous histology (2%

TABLE 4. Tumor Response per RECIST[a]

	Arm A Motesanib + C/P (*n* = 182)	Arm B Placebo + C/P (*n* = 178)
Patients with measurable disease at baseline, *n* (%)	178 (98)	177 (99)
Response assessment, *n* (%)		
Confirmed CR	0 (0)	1 (<1)
Confirmed PR	67 (38)	61 (34)
SD[b]	70 (39)	79 (45)
Progressive disease	15 (8)	20 (11)
Not done[c]	26 (15)	16 (9)
Confirmed objective response (CR or PR), *n* (%)	67 (38)	62 (35)
Difference, % (95% CI)	2.6 (−7.4 to 12.6)	
p value[d]	0.7362	
Responders with measurable disease at baseline, *n* (%)	67 (38)	62 (35)
Duration of response, mo (95% CI)	7.2 (4.8–9.1)	4.4 (4.2–5.6)

C/P, carboplatin/paclitaxel; CR, complete response; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors; CI, confidence interval.

[a]Assessed by investigators per RECIST version 1.0. The analysis set included all randomized patients who had squamous histology. The denominator for all response categories was the number of patients with measurable disease at baseline.

[b]Patients with an assessment of PR or CR not confirmed ≥4 weeks later were classified as having SD.

[c]Patients for whom imaging was not performed at the scheduled assessment of response.

[d]From Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

versus 0.3%, respectively), it was similar among patients with squamous NSCLC who received sorafenib and those who did not (2% in each arm). Finally, in a phase 2 study of vandetanib plus C/P for the treatment of advanced NSCLC, grade ≥3 hemoptysis did not occur in the vandetanib arm.[11] It has been speculated that the increased risk of bleeding may be a consequence of the greater likelihood of squamous tumors to be centrally located and/or to cavitate, suggesting that tumor histology is an important factor to consider in the toxicity evaluation of any new drug being developed in this setting.[10] Data collected from the patient cohort with squamous histology in the MONET1 study did not yield sufficient information to investigate this hypothesis further. Interestingly, in a phase 3 study of the vascular disrupting agent ASA404 in patients with squamous or nonsquamous NSCLC, treatment with ASA404 plus C/P was not associated with increased toxicity compared with placebo plus paclitaxel (efficacy outcomes were also not improved).[32] The biologic mechanisms by which VEGF pathway inhibitors might induce bleeding remain uncertain. It is possible that differences in mechanisms of action and effects on tumor blood vessels of different VEGF pathway inhibitors might influence the incidence of bleeding across studies.

Although there was no evidence of improved OS, PFS, or ORR among patients in Arm A versus Arm B, the results must be interpreted with caution because treatment duration with motesanib in the squamous cohort was relatively short: the median was 2.2 months (67 days), compared with 4.1 months for patients in the nonsquamous cohort.[21] The short treatment duration was largely a consequence of the decision to terminate motesanib treatment among patients with squamous histology, but early discontinuation due to toxicity may also have contributed. Clearly, the limited exposure to motesanib confounds evaluation of its antitumor activity in squamous NSCLC and makes comparison with results from other studies of VEGF pathway inhibitors in this setting difficult.[11–13] A study evaluating C/P plus vandetanib or placebo demonstrated a trend toward improved PFS (HR, 0.76; 95% CI, 0.32–1.82), but not OS (HR, 1.40; 95% CI, 0.54–3.60) among patients with squamous histology who received vandetanib.[11] Similarly, PFS was longer (HR, 0.66) among patients with squamous histology who received cediranib in the BR.24 study, but there was no statistically significant difference from the overall study cohort.[12] By contrast, in the ESCAPE study, OS was shorter (8.9 versus 13.7 months, respectively; HR, 1.85; 95% CI, 1.22–2.81) and nonspecific toxicity rates were higher among patients with squamous NSCLC who received sorafenib compared with placebo.[13] Therefore, patients with squamous histology who were originally included in the NExUS trial of gemcitabine/cisplatin with or without sorafenib were discontinued as a precaution.[14] Considering the inconsistent evidence of improvements from these studies (only 18% to 24% [*n* = 42–223] of enrolled patients had squamous histology), it is unclear whether a positive risk-benefit profile can be achieved with VEGF pathway inhibitors in combination with chemotherapy in squamous NSCLC.

Currently available data raise questions about the future of these agents as treatment options for patients with squamous histology. The data indicate an increased risk of bleeding, at least with some VEGF pathway inhibitors, and this consequently compromises the ability to evaluate efficacy. If additional studies of VEGF pathway inhibitors are conducted, patients with squamous histology should be evaluated separately from those with nonsquamous histology. A recent study found that elevated VEGF was associated with better outcomes in patients with squamous histology, but not adenocarcinoma histology.[33] These results suggest a different relationship between squamous tumors and angiogenic pathways that might explain the differing response to VEGF inhibition in patients with squamous and nonsquamous histology. Because they represent one of the largest cohorts of patients with squamous histology reported to date, the results from the MONET1 squamous cohort provides an important benchmark for future studies. Alternative approaches for adding VEGF pathway inhibitors to standard-of-care regimens should also be considered. For example, the open-label BRIDGE study, which enrolled only patients with squamous NSCLC, evaluated C/P chemotherapy with bevacizumab introduced at the third chemotherapy cycle and continued as maintenance therapy after the sixth cycle. One of 31 treated patients had severe pulmonary hemorrhage.[34]

In summary, results from patients with squamous histology enrolled in the MONET1 study found higher early mortality and unacceptable toxicity among patients receiving motesanib. The results suggest that, in patients with NSCLC, tumor histology plays an important role in determining not only efficacy, but also toxicity. The results represent one of

the largest datasets describing squamous NSCLC in a clinical study and provide an important benchmark of outcomes in squamous NSCLC that may inform the development and interpretation of future studies.

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