2. SYNOPSIS

Name of Sponsor: Amgen

Name of Finished Product: motesanib (AMG 706)

Name of Active Ingredient: motesanib diphosphate

Title of Study: A Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind Trial of AMG 706 in Combination with Paclitaxel and Carboplatin for Advanced Non-small Cell Lung Cancer

Investigator(s) and Study Center(s): This study was conducted at 208 centers. A total of 198 centers in 32 countries enrolled subjects with non-squamous non-small cell lung cancer (NSCLC). Centers and principal investigators are listed in Appendix 4.

Publication(s): None

Study Period: This clinical study report includes results from 05 July 2007 (date that the first subject was enrolled) to 03 February 2011 (primary analysis data cutoff date [PADCD]). The PADCD was the date on which 742 deaths in the overall non-squamous population and 593 deaths in the adenocarcinoma subpopulation were confirmed. Results obtained after the PADCD, including survival follow-up, will be reported separately.

Development Phase: Phase 3

Objectives:

The primary objective of this study was to determine if treatment with motesanib in combination with paclitaxel and carboplatin improves overall survival (OS) compared with treatment with placebo in combination with paclitaxel and carboplatin in subjects with advanced non-squamous NSCLC and in subjects with adenocarcinoma histology (adenocarcinoma subpopulation).

Secondary objectives of this study were to evaluate: progression-free survival (PFS) time, the association of motesanib treatment-induced placental growth factor (PlGF) increase with OS in subjects with non-squamous NSCLC and adenocarcinoma, objective tumor response rate (ORR) (in subjects with measurable disease only), duration of response, evaluation of the same disease endpoints and OS in subjects with non-squamous, nonadenocarcinoma histologies (hereinafter referred to as nonadenocarcinoma); safety and tolerability of motesanib in combination with paclitaxel and carboplatin compared with placebo in combination with paclitaxel and carboplatin in subjects with non-squamous NSCLC and adenocarcinoma histologies; the pharmacokinetics of motesanib and metabolites when administered with paclitaxel and carboplatin (in approximately 250 subjects at selected centers); and the pharmacokinetics of carboplatin (total and unbound platinum concentrations) when administered in combination with paclitaxel and motesanib or placebo (in approximately 20 to 30 subjects at selected centers outside of the European Union [EU]).

Exploratory objectives were to investigate: [redacted]

Methodology:

This was a phase 3, multicenter, randomized, placebo-controlled, double-blind study examining the efficacy and tolerability of motesanib when administered with paclitaxel and carboplatin. Subjects with unresectable stage IIIB with pericardial or pleural effusion or stage IV or recurrent

non-squamous NSCLC were randomized in a 1:1 ratio to receive either 125 mg motesanib or matching placebo orally once daily in combination with a standard paclitaxel and carboplatin chemotherapy regimen. Randomization was stratified by stage (stage IIIB vs stage IV or recurrent), weight loss (< 5% vs ≥ 5% in the previous 6 months prior to randomization), sex (male vs female), and prior adjuvant chemotherapy (yes vs no). Subjects received paclitaxel and carboplatin chemotherapy every 3 weeks ± 3 days up to a maximum of 6 cycles. Subjects received chemotherapy (paclitaxel and carboplatin) with either motesanib or placebo until disease progression or drug (motesanib or placebo) intolerability, withdrawal, or death. Following withdrawal or completion of chemotherapy, subjects could continue to receive placebo or motesanib as monotherapy for maintenance.

Study visits during the chemotherapy cycles and during the monotherapy phase were performed every 3 weeks ± 3 days. Radiological imaging to assess disease status was performed every 6 ± 1 weeks until disease progression. Adverse events, concomitant medications, vital signs, clinical laboratory parameters, biomarker and pharmacokinetic sampling, and PROs were evaluated at regular, prespecified intervals.

Subjects discontinued study treatment if they developed disease progression. Subjects who discontinued study treatment before disease progression are being followed for progression of disease until documented disease progression, death, or full consent withdrawal, up to 36 months after the last subject was randomized. All subjects are being followed for survival by clinic visit or telephone every 3 months ± 2 weeks from the safety follow-up visit until up to 36 months after the last subject was randomized.

Number of Subjects Planned: 1400 subjects total; 1060 subjects with non-squamous NSCLC

Number of Subjects Enrolled: 1450 subjects total; 1090 subjects with non-squamous NSCLC

Diagnosis and Main Criteria for Eligibility: Eligible subjects met the following criteria: adult with histologically confirmed, measurable or nonmeasurable, unresectable stage IIIB with pericardial or pleural effusion or stage IV or recurrent non-squamous NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; adequate organ function; life expectancy ≥ 3 months; and no prior chemotherapy for advanced non-squamous NSCLC, prior adjuvant chemotherapy for non-squamous NSCLC within 52 weeks, or prior chemoradiation for locally advanced stage III disease.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: In this study, investigational product referred to either motesanib or placebo, with placebo considered the reference therapy. Study treatment referred to investigational product or the protocol-specified chemotherapeutics, paclitaxel and carboplatin.

Investigational Product

Motesanib was provided as white to light brown, film-coated tablets containing 25 mg motesanib diphosphate and the following excipients: microcrystalline cellulose, pregelatinized starch, hydroxypropyl methylcellulose, crospovidone, colloidal silicon dioxide, glyceryl behenate, magnesium stearate, and Opadry II Beige. Placebo was provided in identical containers and was identical in formulation (excluding the drug content) to the active motesanib product.

Subjects self-administered motesanib 125 mg or placebo (5 tablets) orally once daily in the morning on an empty stomach (ie, no food or liquids, except water, for 2 hours before and 1 hour after dosing), unless otherwise indicated. Investigational product was taken after clinical assessments were performed and before chemotherapy was administered on days that the subject returned to the clinic. Lot numbers for motesanib and placebo used in this study are provided in Appendix 18.

Chemotherapy Regimen

Subjects in the placebo and motesanib arms were administered 200 mg/m^2 paclitaxel as a 3-hr ± 30-min intravenous (IV) infusion and carboplatin, to a target area under the concentration-time curve (AUC) of 6 mg/mL x min, as an IV infusion over 30 ± 10 min on the first day of every 3-week cycle, starting with day 1 of cycle 1. Commercially available paclitaxel and carboplatin were obtained and administered by the investigators for this study.

Duration of Treatment: Subjects received motesanib or placebo daily beginning on day 1 of the first cycle of chemotherapy until disease progression or drug (motesanib or placebo) intolerability, withdrawal or death. Subjects received paclitaxel and carboplatin chemotherapy on the first day of every 3-week (± 3 days) cycle, up to a maximum of 6 cycles.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: As described above, placebo was the reference therapy in this study.

Study Endpoints:

Primary Efficacy Endpoint:

- OS time

Secondary Efficacy Endpoints:

- PFS time
- OS time in the PlGF analysis set
- ORR (complete or partial response) according to modified Response Evaluation Criteria in Solid Tumors (RECIST) in subjects with measurable disease at baseline
- Duration of response (calculated only for those subjects who responded)
- Pharmacokinetics of motesanib (eg, minimum and maximum observed motesanib concentrations [C_{min} and C_{max}, respectively] and metabolite concentrations) when administered in combination with paclitaxel and carboplatin
- Pharmacokinetics (eg, C_{max}) of carboplatin (total and unbound platinum concentrations) when administered in combination with paclitaxel and motesanib or placebo

Safety Endpoints:

- Subject incidence of treatment-emergent adverse events
- Changes in laboratory values

Exploratory Endpoints:

- [redacted]

Statistical Methods:

Analyses were conducted separately for subjects with non-squamous NSCLC and the subset of subjects with adenocarcinoma. In the original study protocol, subjects with squamous NSCLC were also permitted to enroll in the study, but a study protocol amendment excluded these subjects from enrollment following the recommendation of DMC which noted an unacceptable rate of hemoptysis in subjects with squamous NSCLC; results of exploratory analyses of subjects with squamous NSCLC are provided in Appendix 23.

Summary statistics were provided for all safety, efficacy, pharmacokinetic, and biomarker data by treatment group. For continuous variables, the mean, standard deviation, median, first and third quartiles, minimum, and maximum were calculated. For categorical variables, the frequency and percentage in each category were determined. Graphical summaries of selected endpoints were also presented.

The primary endpoint was OS time, which was calculated from randomization to the date of death due to any cause. A log-rank test was used to compare the treatment groups with the following stratification factors: stage of disease at enrollment (IIIB vs IV/recurrent), weight loss in the

previous 6 months (< 5% vs ≥ 5%), prior adjuvant chemotherapy, and sex. An alpha-split level approach was used for testing of the non-squamous (3%) and adenocarcinoma (2%) populations in parallel. A stratified Cox model was used to estimate the hazard ratio and 95% confidence interval (CI) for OS using the same stratification factors.

Progression-free survival time was analyzed using same methodology as OS (stratified log-rank test and stratified Cox model). ORR was compared between treatment groups by Cochran-Mantel-Haenszel test with the stratification factors as covariates, based on the subjects with measurable disease. Two-sided 95% CIs were calculated for the differences in ORR between treatment groups using the normal approximation to the binomial distribution. Descriptive statistics were provided for best overall tumor response for each treatment group, based on the subjects with measurable disease. For duration of response, Kaplan-Meier curves were presented for each treatment group. No statistical testing was performed to compare the treatment groups for this endpoint. The same alpha-split levels were used for the secondary efficacy endpoints for the non-squamous (3%) and adenocarcinoma (2%) populations.

Descriptive statistics of the individual C_{min} values of motesanib and M4 on Day1 of Cycles 3 and 5 and every third visit thereafter were calculated (mean, standard deviation, median, minimum, and maximum). In addition, C_{max} values of motesanib on Day 1 of Cycle 3 were calculated. Descriptive statistics of the individual C_{max} values on Day 1 of Cycles 3 and 5 of carboplatin (total and unbound platinum concentrations) when administered in combination with paclitaxel and motesanib or placebo were also calculated.

Assessment of OS in the PlGF analysis set was evaluated first using a Cox model with the log-transformed PlGF fold change between baseline and week 4 as a continuous variable with no other covariates in the model to provide the hazard ratio (and 95% CI) associated with each unit increase of log-transformed PlGF fold change. Next, the log-transformed PlGF fold change between baseline and week 4 was assessed as a binary variable (≥ 2-fold vs < 2-fold PlGF change) using an unadjusted log-rank test. The hazard ratio and 95% CI for the PlGF status and Kaplan-Meier curves were presented with the estimates for OS and associated 95% CIs in the rates at selected time points for each PlGF status. Data from the PlGF undetermined subjects were also described.

Adverse events were coded in the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 by system organ class and a preferred term, and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Amgen has adopted the Council for International Organizations of Medical Sciences definition of an adverse event of interest (EOI), which is “a noteworthy event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.” Subject incidence rates of treatment-emergent adverse events, treatment-emergent EOIs, serious adverse events, grade ≥ 3 adverse events, and adverse events leading to motesanib or placebo discontinuation or study withdrawal were tabulated by system organ class and preferred term. Narratives of deaths and serious adverse events were provided. Additional tables of adverse events were provided for subgroups defined by age, sex, and race. Laboratory parameters were summarized over time using descriptive statistics for recorded values and change from baseline. Shift tables displayed the incidence of shift of toxicity grade (CTCAE Version 3.0) in recorded values from baseline to “worst” on-study value.

Summary of Results:

Subject Disposition:

A total of 1090 subjects (541 motesanib, 549 placebo) with non-squamous NSCLC were enrolled and included in the Non-squamous Full Analysis Set. Actual follow-up time was a median of 11.0 and 10.3 months in the motesanib and placebo arms, respectively. Reasons for ending study (motesanib, placebo) were death (64%, 70%), full consent withdrawn (8%, 7%), lost to follow-up (3%, 3%), administrative decision (<1%, 0%), and other reasons (<1%, 0%). Most subjects (65% motesanib, 68% placebo) completed safety follow-up.

Of the 1090 randomized subjects with non-squamous NSCLC, 890 (448 motesanib, 442 placebo) were included in the adenocarcinoma subpopulation (ie, the Adenocarcinoma Full Analysis Set); similar results were observed in the disposition of subjects in the Adenocarcinoma Full Analysis Set.

Baseline Demographics (Non-squamous Full Analysis Set):

		Placebo N = 549	Motesanib N = 541
Sex:	Female	213 (39%)	207 (38%)
	Male	336 (61%)	334 (62%)
Age (years):	Median (range)	60 (21, 84)	60 (23, 87)
Ethnicity (Race):	White/Caucasian	353 (64%)	362 (67%)
	Asian (excluding Japanese)	97 (18%)	84 (16%)
	Japanese	51 (9%)	55 (10%)
	Hispanic/Latino	38 (7%)	28 (5%)
	Black/African American	7 (1%)	9 (2%)
	Aborigine	1 (<1%)	1 (<1%)
	Other	2 (<1%)	2 (<1%)

Efficacy Results:

The primary efficacy endpoint, OS from randomization to the date of death, was not significantly different between treatment groups. In the Non-squamous Full Analysis Set, median OS time in the motesanib and placebo arms was 13.0 months (95% CI: 11.2, 14.0 months) and 11.0 months (95% CI: 10.1, 12.4 months), respectively. The hazard ratio for OS (motesanib/placebo) was 0.897 (95% CI: 0.776, 1.035) in the stratified Cox proportional hazards model (log-rank p = 0.1366) and 0.901 (95% CI: 0.781, 1.040) in the unstratified Cox proportional hazards model (log-rank p = 0.1544). In the Adenocarcinoma Full Analysis Set, median OS time in the motesanib and placebo arms was 13.5 months (95% CI: 11.3, 14.7 months) and 11.0 months (95% CI: 9.9, 12.4 months), respectively. The hazard ratio for OS (motesanib/placebo) was 0.878 (95% CI: 0.748, 1.031) in the stratified Cox proportional hazards model (log-rank p = 0.1129) and 0.880 (95% CI: 0.751, 1.032) in the unstratified Cox proportional hazards model (log-rank p = 0.1163). In subgroup analyses, the hazard ratio for OS favored motesanib over placebo among subjects who were non-white or were from the “rest of the world” (ie, not from the US, Canada, Australia, or the EU).

Because the primary endpoint did not achieve statistical significance, formal testing of the secondary study endpoints was not done. Thus, the results provided for secondary efficacy endpoints in this report are descriptive and are not intended for inferential purposes. Median PFS time in the motesanib and placebo arms was 5.6 months (95% CI: 5.4, 6.2 months) and 5.4 months (95% CI: 4.7, 5.5 months), respectively. The hazard ratio for PFS (motesanib/placebo) was 0.785 (95% CI: 0.684, 0.901) in the stratified Cox proportional hazards model (log-rank p = 0.0006) and 0.776 (95% CI: 0.678, 0.890) in the unstratified Cox proportional hazards model (log-rank p = 0.0003). In the motesanib and placebo arms, confirmed objective response rates were 40% and 26% (p < 0.0001), respectively. The median duration of response by Kaplan-Meier analysis was 5.8 months (95% CI: 5.3, 6.5 months) in the motesanib arm and 5.0 months (95% CI: 4.4, 5.6 months) in the placebo arm. PlGF fold change (continuous or binary) was not associated with OS, PFS, or objective response rate.

Because the primary endpoint did not achieve statistical significance in either the Non-Squamous Full Analysis Set or the Adenocarcinoma Full Analysis Set, planned secondary efficacy analyses of the nonadenocarcinoma population were not conducted. Results of exploratory analyses of subjects with squamous NSCLC are provided in Appendix 23; the other planned exploratory analyses were not conducted.

Pharmacokinetics Results:

Following the 125 mg once daily dosing of motesanib in subjects with non-squamous NSCLC, the median motesanib C_{min} values on Cycle 3 Day 1 and Cycle 5 Day 1 were 6.38 (0.00 to 77.9) and 5.27 (0.00 to 26.1) ng/mL, respectively, and the median C_{max} value on Cycle 3 Day 1 was 225 (20.2 to 1030) ng/mL. The major metabolite M4 median C_{min} values on Cycle 3 Day 1 and Cycle 5 Day 1 were 23.5 (0.00 to 176) and 11.0 (0.00 to 200) ng/mL, respectively. The M4 C_{min} levels were higher than motesanib, with median M4/motesanib C_{min} ratios of 2.67 and 2.40 on Cycle 3 and Cycle 5, respectively.

Bile samples were collected from 3 subjects after 125 mg motesanib administration in combination with paclitaxel and carboplatin. Motesanib and motesanib glucuronide had similar concentrations in bile. M4 concentrations were only 10% of the motesanib concentration in the bile.

Coadministration of motesanib with carboplatin appears to slightly increase the total and unbound plasma concentration of carboplatin. The total and unbound plasma carboplatin concentrations from Cycle 3 Day 1 and Cycle 5 Day 1 were 12% to 30% higher in the presence of motesanib from subjects with carboplatin pharmacokinetic data.

Patient-Reported Outcomes Results:

Safety Results:

Treatment-emergent adverse events were reported for 96% of subjects in both treatment arms. A higher incidence of adverse events was reported in the motesanib arm compared with the placebo arm (≥ 5%) in the following System Organ Classes: blood and lymphatic system disorders, endocrine disorders, gastrointestinal disorders, general disorders and administration site conditions, hepatobiliary disorders, infections and infestations, investigations, metabolism and nutrition disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders, and vascular disorders. Differences of ≥ 5% were noted between the treatment arms in the subject incidence of adverse events (all were higher in the motesanib arm) in the following preferred terms (motesanib vs placebo, respectively): diarrhea (48% vs 22%), nausea (42% vs 33%), decreased appetite (35% vs 27%), vomiting (33% vs 26%), fatigue (33% vs 28%), neutropenia (28% vs 20%), hypertension (26% vs 6%), thrombocytopenia (21% vs 15%), rash (18% vs 11%), weight decreased (17% vs 9%), abdominal pain (17% vs 6%), headache (15% vs 9%), stomatitis (11% vs 5%), and proteinuria (9% vs 3%).

The subject incidence of grade of 3, 4, or 5 adverse events was 73% in motesanib-treated subjects and 59% in placebo-treated subjects. The incidence of grade 3, 4, or 5 events was ≥ 5% higher in the motesanib arm compared with the placebo arm in the following System Organ Classes: blood and lymphatic system disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, investigations, metabolism and nutrition disorders, and vascular disorders. Differences of ≥ 5% were noted between the treatment arms in the subject incidence of grade 3, 4, or 5 adverse events (all were higher in the motesanib arm) in the following preferred terms (motesanib vs placebo, respectively): neutropenia (22% vs 15%), diarrhea (9% vs 1%), and hypertension (7% vs 1%).

Serious adverse events were reported in 49% of subjects treated with motesanib and 34% of subjects treated with placebo. The incidence of serious adverse events was ≥ 5% higher in the motesanib arm compared with the placebo arm in the following System Organ Classes: blood and lymphatic system disorders, gastrointestinal disorders, hepatobiliary disorders, and

metabolism and nutrition disorders. A ≥ 5% difference in the subject incidence of serious adverse events was noted between the treatment arms for the preferred term of diarrhea (6% motesanib vs 1% placebo).

Fatal adverse events occurring on study (ie, within 30 days of the last dose of study treatment) were reported for 14% of subjects treated with motesanib and 9% of subjects treated with placebo. The subject incidence of fatal adverse events occurring within 30 days of the first dose of protocol-specified treatment was 4% of subjects treated with motesanib and 3% of subjects treated with placebo. A higher number of subjects treated with motesanib than subjects treated with placebo had fatal adverse events for the following preferred terms (motesanib vs placebo): pneumonia (7 vs 0), general physical health deterioration (6 vs 1), respiratory failure (5 vs 2), and hemoptysis (3 vs 0). In several of these subjects, medical histories and comorbid conditions were present as contributing factors to the fatal adverse events. Fewer subjects treated with motesanib than subjects treated with placebo had fatal adverse events for the following preferred terms (motesanib vs placebo): pulmonary embolism (3 vs 6) and cardio-respiratory arrest (1 vs 4).

Overall, 31% and 15% of subjects treated with motesanib and placebo, respectively, had adverse events leading to discontinuation of investigational product. The most frequently reported (≥ 1%) events leading to discontinuation of investigational product in the motesanib arm were diarrhea (3%), cholecystitis (2%), abdominal pain (1%), hemoptysis (1%), asthenia (1%), and neutropenia (1%). The subject incidence of adverse events leading to discontinuation of chemotherapy (carboplatin and/or paclitaxel) was higher in the motesanib arm compared with the placebo arm (21% vs 14%). The most frequently reported (≥ 1%) events leading to discontinuation of chemotherapy in the motesanib arm were peripheral sensory neuropathy (2%), peripheral neuropathy (2%), thrombocytopenia (2%), neutropenia (1%), and fatigue (1%).

Treatment-emergent EOIs (non-infectious diarrhea, hypertension, reversible posterior leukoencephalopathy syndrome events, gallbladder related disorders, arterial thromboembolic events, thromboembolic events, cardiac failure, hypothyroidism, hemorrhage events, gastrointestinal perforation, proteinuria, acute pancreatitis, drug related hepatic disorders, hematopoietic cytopenias, and peripheral neuropathy) were reported for 92% of subjects treated with motesanib and 90% of subjects treated with placebo.

The incidence of events was ≥ 5% higher in the motesanib arm compared with the placebo arm in the following EOIs: non-infectious diarrhea (48% vs 23%), hypertension (27% vs 6%), gallbladder related disorders (8% vs <1%), hypothyroidism (7% vs 2%), hemorrhage events (23% vs 15%), proteinuria (10% vs 4%), drug related hepatic disorders (14% vs 7%), hematopoietic cytopenias (52% vs 45%), and peripheral neuropathy (53% vs 48%).

While the incidence of preferred terms retrieved using the broad search strategy for acute pancreatitis was higher in the motesanib arm compared to placebo (58% vs 47%, respectively), many of the terms retrieved were non-specific (nausea, vomiting, abdominal pain, etc). The incidence of preferred terms retrieved using the narrow search strategy for acute pancreatitis was similar for both treatment groups (<1% for both).

Using a pre-specified case definition, 1 motesanib-treated subject had a confirmed reversible posterior leukoencephalopathy event compared with none in the placebo arm. The subject incidences for all other EOIs were generally similar across treatment arms.

Adverse events known to be associated with carboplatin administration were also reviewed. The subject incidence of adverse events of neutropenia and thrombocytopenia, as well as the subject incidence of nausea and vomiting, was higher in the motesanib arm compared with placebo. The subject incidence of grade 3 and 4 neutropenia and thrombocytopenia laboratory abnormalities, however, was similar between the 2 arms.

In general, changes in laboratory values were consistent with results observed in previous motesanib studies (motesanib diphosphate Investigator's Brochure).

The changes observed in systolic and diastolic blood pressure were consistent with the more frequent reports of hypertension in subjects treated with motesanib when compared to subjects treated with placebo or bevacizumab.

Conclusions:

The addition of motesanib to combination chemotherapy with paclitaxel and carboplatin did not increase OS significantly compared with the addition of placebo, either among subjects with non-squamous NSCLC or in the subgroup of subjects with adenocarcinoma. The trough level of M4 was higher than the motesanib level in subjects with non-squamous NSCLC. Coadministration of motesanib with carboplatin appears to slightly increase the total and unbound plasma concentration of carboplatin. Adverse events with a greater than or equal to 5% increase in the motesanib arm when compared to the control arm warrant consideration as identified risks for motesanib either independently, ie, diarrhea, hypertension, and proteinuria, or in combination with paclitaxel, ie, neutropenia, thrombocytopenia, nausea, decreased appetite, vomiting, decreased weight loss, abdominal pain, stomatitis, headache, fatigue, and rash.

A significant association was not seen between PlGF change and OS. Selected secondary efficacy endpoints such as PFS and objective response favored the addition of motesanib, but these secondary analyses were not intended for inferential purposes.

2. SYNOPSIS

Name of Sponsor: Amgen

Name of Finished Product: motesanib (AMG 706)

Name of Active Ingredient: motesanib diphosphate

Title of Study: A Phase 3, Multicenter, Randomized, Placebo-controlled, Double-blind Trial of AMG 706 in Combination With Paclitaxel and Carboplatin for Advanced Non-small Cell Lung Cancer

Investigator(s) and Study Center(s): This study was conducted at 208 centers worldwide. A total of 198 centers in 32 countries enrolled subjects with non-squamous non-small cell lung cancer (NSCLC). Centers and principal investigators are listed in Section 16.1.4.

Publication(s): Scagliotti GV, Vynnychenko I, Park K, et al. 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. *J Clin Oncol*. 2012; 30(23):2829-2836.

Scagliotti G et al. An international, randomized, placebo-controlled, double-blind phase 3 study (MONET1) of motesanib plus carboplatin/paclitaxel (C/P) in patients with advanced nonsquamous non–small-cell lung cancer (NSCLC). *J Clin Oncol.* 2011;29(18s). Abstract LBA7512.

Ichinose et al. Phase 3 study (MONET1) of motesanib plus carboplatin/paclitaxel (C/P) in patients with advanced nonsquamous non-small-cell lung cancer (NSCLC): Asian subgroup analysis. *J Clin Oncol.* 2012;30(15s). Abstract 7549.

Study Period: 05 July 2007 (first subject enrolled) to 14 December 2012 (last subject completed follow-up)

Development Phase: Phase 3

Objectives:

Primary objective:

- to determine if treatment with motesanib in combination with paclitaxel and carboplatin improves overall survival (OS) compared with treatment with placebo in combination with paclitaxel and carboplatin in subjects with advanced non-squamous non-small cell lung cancer (NSCLC) and in subjects with adenocarcinoma histology (adenocarcinoma subpopulation)

Secondary objectives:

- to evaluate progression-free survival (PFS) time, objective tumor response rate (ORR) (in subjects with measurable disease only), and duration of response in subjects with non-squamous NSCLC and in subjects with adenocarcinoma histology
- to evaluate the association of motesanib treatment-induced placental growth factor (PlGF) increase with OS in subjects with non-squamous NSCLC and adenocarcinoma
- to evaluate the safety and tolerability of motesanib in combination with paclitaxel and carboplatin compared with placebo in combination with paclitaxel and carboplatin in subjects with non-squamous NSCLC and adenocarcinoma histologies

- to evaluate OS, PFS, motesanib treatment-induced PlGF increase association with OS, ORR (only in subjects with measurable disease) and duration of response in subjects with non-squamous nonaddenocarcinoma histology (herein after referred to as nonadenocarcinoma)
- to evaluate the pharmacokinetics (PK) of motesanib and metabolites when administered with paclitaxel and carboplatin (in approximately 250 subjects at selected centers)
- to evaluate the PK (maximum observed concentration [C_{max}]) of carboplatin (total and unbound platinum concentrations) when administered in combination with paclitaxel and motesanib or placebo (in approximately 20 to 30 subjects at selected centers outside of the European Union [EU])

Exploratory objectives:

- [redacted]

Results for the primary analysis were based on data collected from 05 July 2007 (date that the first subject was enrolled) to 03 February 2011 (primary analysis data cutoff date [PADCD]). The PADCD was the date on which 742 deaths in the overall non-squamous population and 593 deaths in the adenocarcinoma subpopulation were confirmed.

At the time of data cutoff for the primary analysis, 19 subjects were still on treatment or in study follow-up. Updated safety and efficacy results for PFS and OS, through the study completion date (14 December 2012) are included in this synopsis clinical study report (CSR).

Methodology: This was a phase 3, multicenter, randomized, placebo-controlled, double-blind study examining the efficacy and tolerability of motesanib when administered with paclitaxel and carboplatin, as described in Protocol Section 3 (Section 16.1.1 of this report). Subjects with unresectable stage IIIB with pericardial or pleural effusion, or with stage IV or recurrent non-squamous NSCLC were randomized in a 1:1 ratio to receive either 125 mg motesanib or matching placebo orally once daily in combination with a standard paclitaxel and carboplatin chemotherapy regimen. Randomization was stratified by stage (stage IIIB vs stage IV or recurrent), weight loss (< 5% vs ≥ 5% in the previous 6 months prior to randomization), sex, and prior adjuvant chemotherapy (yes vs no). Subjects received paclitaxel and carboplatin chemotherapy every 3 weeks ± 3 days up to a maximum of 6 cycles. Subjects received chemotherapy (paclitaxel and carboplatin) with either motesanib or placebo until disease progression or drug (motesanib or placebo) intolerability, withdrawal, or death. Following withdrawal or completion of chemotherapy, subjects could continue to receive placebo or motesanib as monotherapy for maintenance.

Study visits during the chemotherapy cycles and during the monotherapy phase were performed every 3 weeks ± 3 days. Radiological imaging to assess disease status was performed every 6 ± 1 weeks until disease progression. Adverse events, concomitant medications, vital signs, clinical laboratory parameters, biomarker and pharmacokinetic sampling, and patient-reported outcomes (PROs) were evaluated at regular, prespecified intervals.

Subjects discontinued study treatment if they developed disease progression. Subjects who discontinued study treatment before disease progression were followed until documented disease progression, death, or full consent withdrawal, up to 36 months after the last subject was randomized. All subjects were followed for survival by clinic

visit or telephone every 3 months ± 2 weeks from the safety follow-up visit until up to 36 months after the last subject was randomized.

Number of Subjects Planned: 1400 subjects total; 1060 subjects with non-squamous NSCLC

Number of Subjects Enrolled: 1450 subjects total; 1090 subjects with non-squamous NSCLC

Diagnosis and Main Criteria for Eligibility: Men or women aged ≥ 18 years with histologically confirmed, measurable or nonmeasurable, unresectable stage IIIB with pericardial or pleural effusion or stage IV or recurrent non-squamous NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; adequate organ function; life expectancy ≥ 3 months; and no prior chemotherapy for advanced non-squamous NSCLC, prior adjuvant chemotherapy for non-squamous NSCLC within 52 weeks, or prior chemoradiation for locally advanced stage III disease.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: In this study, investigational product referred to either motesanib or placebo, with placebo considered the reference therapy. Study treatment referred to investigational product or the protocol-specified chemotherapeutics, paclitaxel and carboplatin.

Investigational Product

Motesanib was provided as tablets containing 25 mg motesanib diphosphate. Placebo was provided in identical containers and was identical in formulation (excluding the drug content) to the active motesanib product.

Subjects self-administered motesanib 125 mg or placebo (5 tablets) orally once daily in the morning on an empty stomach (ie, no food or liquids, except water, for 2 hours before and 1 hour after dosing), unless otherwise indicated. Investigational product was taken after clinical assessments were performed and before chemotherapy was administered on days that the subject returned to the clinic.

Manufacturing lot numbers for motesanib were [redacted].

Manufacturing lot numbers for placebo were [redacted].

Chemotherapy Regimen

Subjects in the placebo and motesanib arms were administered 200 mg/m^2 paclitaxel as a 3-hr ± 30-min intravenous (IV) infusion and carboplatin, to a target area under the concentration-time curve (AUC) of 6 mg/mL x min, as an IV infusion over 30 ± 10 min on the first day of every 3-week cycle, starting with day 1 of cycle 1. Commercially available paclitaxel and carboplatin were obtained and administered by the investigators for this study.

Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: As described above, placebo was the reference therapy in this study.

Duration of Treatment: Subjects received motesanib or placebo daily beginning on day 1 of the first cycle of chemotherapy until disease progression or drug (motesanib or

placebo) intolerability, withdrawal or death. Subjects received paclitaxel and carboplatin chemotherapy on the first day of every 3-week (± 3 days) cycle, up to 6 cycles.

Study Endpoints:

Efficacy Endpoints:

Primary Efficacy Endpoint:

- OS time

Secondary Efficacy Endpoints:

- PFS time
- OS time in the PlGF analysis set
- ORR (complete or partial response) according to modified Response Evaluation Criteria in Solid Tumors (RECIST) in subjects with measurable disease at baseline
- Duration of response (calculated only for those subjects who responded)
- PK of motesanib (eg, minimum observed motesanib concentrations [C_{min}] and C_{max}) and metabolite concentrations) when administered in combination with paclitaxel and carboplatin
- PK (eg, C_{max}) of carboplatin (total and unbound platinum concentrations) when administered in combination with paclitaxel and motesanib or placebo

Safety Endpoints:

- Subject incidence of treatment-emergent adverse events
- Changes in laboratory values

[redacted]

Statistical Methods: Detailed information of the statistical analyses can be found in the Statistical Analysis Plan Section 10 (Section 16.1.9 of this report).

Analyses were conducted separately for subjects with non-squamous NSCLC and the subset of subjects with adenocarcinoma. In the original study protocol, subjects with squamous NSCLC were also permitted to enroll in the study, but a study protocol amendment excluded these subjects from enrollment following the recommendation of data monitoring committee (DMC) which noted an unacceptable rate of hemoptysis in subjects with squamous NSCLC; results of exploratory analyses of subjects with squamous NSCLC were provided in Appendix 23 of the primary analysis CSR and final analyses are presented in this report.

Summary statistics were provided for all safety, efficacy, pharmacokinetic, and biomarker data by treatment group. For continuous variables, the mean, standard deviation, median, first and third quartiles, minimum, and maximum were calculated. For

categorical variables, the frequency and percentage in each category were determined. Graphical summaries of selected endpoints were also presented.

The primary endpoint was OS time, which was calculated from randomization to the date of death due to any cause. A log-rank test was used to compare the treatment groups with the following stratification factors: stage of disease at enrollment (IIIB vs IV or recurrent), weight loss in the previous 6 months (< 5% vs ≥ 5%), prior adjuvant chemotherapy, and sex. An alpha-split level approach was used for testing of the non-squamous (3%) and adenocarcinoma (2%) populations in parallel. A stratified Cox model was used to estimate the hazard ratio and 95% confidence interval (CI) for OS using the same stratification factors.

Progression-free survival time was analyzed using same methodology as OS (stratified log-rank test and stratified Cox model). Analyses of other secondary efficacy endpoints were not conducted at final analysis as the primary analysis results were mature.

The schedule of pharmacokinetic assessments and details on the bioanalytical methodology for motesanib, M4, carboplatin (total and unbound), human bile for motesanib concentration, and human bile for M4 concentration are provided in the primary analysis CSR.

Descriptive statistics of the individual motesanib and M4 C_{min} and C_{max} values and individual carboplatin (total and unbound platinum concentrations) C_{max} values were summarized. Details on the pharmacokinetic analysis methods are provided in the CSR for the primary analysis. Because the primary analysis report included a complete PK contribution, only data for 35 new motesanib pharmacokinetic samples and 47 new M4 pharmacokinetic samples received after the primary analysis cutoff are summarized in this report.

Assessments in the PlGF analysis set were only conducted at the primary analysis (see Protocol, Appendix A [Section 16.1.1 of this report]).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0, and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Amgen has adopted the Council for International Organizations of Medical Sciences definition of an adverse event of interest (EOI), which is “a noteworthy event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.” Subject incidence rates of treatment-emergent adverse events, treatment-emergent EOIs, serious adverse events, grade ≥ 3 adverse events, and adverse events leading to investigational product discontinuation or study withdrawal were tabulated by system organ class and preferred term. Narratives of deaths and serious adverse events were provided. Laboratory parameters were summarized over time using descriptive statistics for recorded values and change from baseline.

Summary of Results:

Subject Disposition: At the time of primary analysis, 19 subjects (2%) remained on study drug and 1053 subject (97%) had discontinued (18 subjects [2%] did not receive placebo or motesanib). The most common reasons for ending placebo or motesanib treatment were disease progression (45% motesanib, 64% placebo) and adverse event (28% motesanib, 13% placebo). Reasons for ending study (motesanib, placebo) were death (64%, 70%), consent withdrawn (8%, 7%), lost to follow-up (3%, 3%), administrative decision (< 1%, 0%), and other reasons (< 1%, 0%). Most subjects (65% motesanib, 68% placebo) completed safety follow-up. The most common reasons

for not completing the safety follow-up period were death (16% motesanib, 13% placebo) and consent withdrawn (6%, 7%) (Primary Analysis Report, Table 8-1).

The analysis sets for subjects at final analysis are the same as those in the primary analysis CSR: 1090 subjects (541 motesanib, 549 placebo) with non-squamous NSCLC were enrolled and included in the Non-squamous Full Analysis Set. Actual follow-up time was a median of 48.0 and 45.0 weeks in the motesanib and placebo arms, respectively. Prior to the database lock for final analysis, all subjects discontinued protocol-specified treatment and ended study. Reasons for ending study (motesanib, placebo) were death (76%, 80%), administrative decision (12%, 9%), consent withdrawn (8%, 7%), lost to follow-up (3%, 3%), and other reasons (<1%, <1%). Most subjects (67% motesanib, 70% placebo) completed safety follow-up (Table 14-1.2.1).

Of the 1090 randomized subjects with non-squamous NSCLC, 890 (448 motesanib, 442 placebo) were included in the adenocarcinoma subpopulation (ie, the Adenocarcinoma Full Analysis Set); similar results were observed in the disposition of subjects in the Adenocarcinoma Full Analysis Set (Table 14-1.2.2).

A total of 360 squamous subjects (182 motesanib, 178 placebo) were randomized in this study and are included in the Squamous Full Analysis Set (Table 14-1.2.4).

Subject Demographics: Subject demographics at baseline for the non-squamous Full Analysis Set are presented in Table 1.

Table 1. Subject Demographics

	Placebo (N = 549)	Motesanib (N = 541)	All Subjects (N = 1090)
Sex - n (%)			
Female	213 (39)	207 (38)	420 (39)
Male	336 (61)	334 (62)	670 (61)
Age			
Median (range)	60.0 (21, 84)	60.0 (23, 87)	60.0 (21, 87)
Ethnicity (Race) - n (%)			
White or Caucasian	353 (64)	362 (67)	715 (66)
Asian	97 (18)	84 (16)	181 (17)
Japanese	51 (9)	55 (10)	106 (10)
Hispanic or Latino	38 (7)	28 (5)	66 (6)
Black or African American	7 (1)	9 (2)	16 (1)
Aborigine	1 (<1)	1 (<1)	2 (<1)
Other	2 (<1)	2 (<1)	4 (<1)

Source: Table 14-2.1.5

Efficacy Results:

Efficacy results for the final analysis were consistent with that previously reported in the primary analysis CSR for all analysis sets (Table 2). In the final analysis, 83% of subjects in the placebo arm and 79% of subjects in the motesanib arm were followed to death. The primary efficacy endpoint, OS, was not significantly different between treatment groups. In the Non-squamous Full Analysis Set, median OS time in the

motesanib and placebo arms was 13.0 months (95% CI: 11.3, 14.0 months) and 11.0 months (95% CI: 10.0, 12.3 months), respectively, which is unchanged from the primary analysis. The hazard ratio for OS (motesanib/placebo) was 0.891 (95% CI: 0.779, 1.019) in the stratified Cox proportional hazards model (log-rank p = 0.0906) and 0.901 (95% CI: 0.789, 1.028) in the unadjusted Cox proportional hazards model (log-rank p = 0.1222), which were also very similar to the primary analysis (Table 2). Differences between treatment arms were not significantly different at primary or final analyses.

Table 2. Overall Survival – Non-squamous Full Analysis Set
Final Analysis vs Primary Analysis

	Final Analysis		Primary Analysis	
	Placebo (N = 549)	Motesanib (N = 541)	Placebo (N = 549)	Motesanib (N = 541)
Censored [a] - n (%)	96 (17)	115 (21)	155 (28)	182 (34)
Deaths - n (%)	453 (83)	426 (79)	394 (72)	359 (66)
Overall survival [b] time (months)				
Median (K-M)	11.0	13.0	11.0	13.0
95% CI of median (K-M)	10.0, 12.3	11.3, 14.0	10.1, 12.4	11.2, 14.0
Q1, Q3 (K-M)	5.8, 23.1	6.2, 25.8	5.8, 22.3	6.2, 25.0
Min, Max	0.0+, 54.4+	0.1, 54.4+	0.0+, 37.9+	0.1, 40.7+
Kaplan-Meier estimate survival - % (95% CI)				
6 months	74 (70, 78)	76 (72, 79)	75 (71, 78)	76 (72, 79)
1 year	47 (43, 51)	52 (48, 57)	47 (43, 52)	52 (48, 56)
2 years	24 (20, 28)	27 (23, 31)	22 (18, 27)	26 (22, 31)
Hazard ratio (Motesanib/placebo) [c]		0.891		0.897
95% CI		(0.779, 1.019)		(0.776, 1.035)
P-value based on the stratified log-rank test [d]		0.0906		0.1366
Hazard ratio (Motesanib/placebo) [e]		0.901		0.901
95% CI		(0.789, 1.028)		(0.781, 1.040)
P-value based on the unadjusted log-rank test [f]		0.1222		0.1544

[a] Subjects that have not been reported as dead are included as 'censored'.
[b] Overall survival time is calculated as the number of days from randomization to death or date of censoring.
[c] Hazard ratio estimated using the Cox proportional hazards model stratified by the randomization stratification factors as recorded in the IVR system at time of randomization: stage (stage IIIB vs stage IV or recurrent), weight loss (< 5% vs >=5% in the 6 months prior to randomization), sex (male vs female) and prior adjuvant chemotherapy (yes vs no).
[d] P-value is based on a 2-sided log-rank test stratified by the randomization stratification factors as recorded in the IVR system at time of randomization: stage (stage IIIB vs stage IV or recurrent), weight loss (< 5% vs >=5% in the 6 months prior to randomization), sex (male vs female) and prior adjuvant chemotherapy (yes vs no).
[e] Hazard ratio estimated using an unadjusted Cox proportional hazards model.
[f] P-value is based on a 2-sided unadjusted log-rank test with no stratification factors.
The Non-Squamous Full Analysis Set includes all randomized subjects who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group assigned at randomization, regardless of the treatment received.
K-M=Kaplan-Meier estimate; CI=Confidence Interval; + Indicates the value is a censoring time.

Source: Table 14-4.1.1, Primary Analysis CSR Table 14-04-001-001

In the Adenocarcinoma Full Analysis Set, results were consistent with that previously reported in the primary analysis CSR. The median OS time in the motesanib and placebo arms was 13.5 months (95% CI: 11.4, 14.7 months) and 11.0 months (95% CI: 9.8, 12.4 months), respectively. The hazard ratio for OS (motesanib/placebo) was 0.879 (95% CI: 0.757, 1.021) in the stratified Cox proportional hazards model (log-rank p = 0.0918) and 0.886 (95% CI: 0.765, 1.026) in the unadjusted Cox proportional hazards model (log-rank p = 0.1057) (Table 14-4.1.2).

In the Squamous Full Analysis Set, 151 motesanib subjects (83%) had died compared to 155 placebo subjects (87%) (Table 14-4.1.4). The median OS time in the motesanib and placebo arms was 11.1 months (95% CI: 9.0, 12.8 months) and 10.7 months (95% CI: 9.4, 12.1 months), respectively. The hazard ratio for OS (motesanib/placebo) was 0.865 (95% CI: 0.689, 1.087) in the stratified Cox proportional hazards model (log-rank p = 0.2140) and 0.851 (95% CI: 0.679, 1.065) in the unadjusted Cox proportional hazards model (log-rank p = 0.1591).

Because the primary endpoint did not achieve statistical significance, formal testing of the secondary study endpoints was not done at the primary or the final analysis. Thus, the results provided for the secondary efficacy endpoint of PFS, in this report and in the primary analysis CSR, are descriptive and are not intended for inferential purposes. Results for all other secondary endpoints were provided in the primary analysis CSR (Primary Analysis Report, Section 9.2.2) and are not intended for inferential purposes. There were no additional results at the time of final analysis for these endpoints.

Median PFS time in the motesanib and placebo arms in the Non-squamous Full Analysis Set was 5.6 months (95% CI: 5.4, 6.2 months) and 5.4 months (95% CI: 4.7, 5.5 months), respectively. The same median PFS time was observed at the time of primary analysis. The hazard ratio for PFS (motesanib/placebo) was 0.785 (95% CI: 0.684, 0.900) in the stratified Cox proportional hazards model (log-rank p = 0.0005) and 0.774 (95% CI: 0.676, 0.886) in the unadjusted Cox proportional hazards model (log-rank p = 0.0002) (Table 14-4.2.1).

Similar results for PFS were seen in the Adenocarcinoma Full Analysis Set. Median PFS time in the motesanib and placebo arms was 5.6 months (95% CI: 5.4, 6.4 months) and 5.4 months (95% CI: 4.7, 5.5 months), respectively. The hazard ratio for PFS (motesanib/placebo) was 0.779 (95% CI: 0.668, 0.907) in the stratified Cox proportional hazards model (log-rank p = 0.0013) and 0.766 (95% CI: 0.659, 0.890) in the unadjusted Cox proportional hazards model (log-rank p = 0.0005) (Table 14-4.2.2).

In the Squamous Full Analysis Set, 114 subjects (63%) in the motesanib arm had a PFS event compared to 121 subjects (68%) in the placebo arm (Table 14-4.2.4). Of these PFS events, 73 (40%) in the motesanib arm and 99 (56%) in the placebo arm were progressive disease. The associated hazard ratio (motesanib/placebo) and CI for the treatment effects were, stratified hazard ratio = 0.848 with 95% CI = (0.650, 1.105) and p = 0.2294; unadjusted hazard ratio = 0.846 with 95% CI = (0.653, 1.096) and p = 0.2104.

Because the primary endpoint did not achieve statistical significance in either the Non-Squamous Full Analysis Set or the Adenocarcinoma Full Analysis Set, planned secondary efficacy analyses of the nonadenocarcinoma population were not conducted. Results of exploratory analyses of subjects with squamous NSCLC are provided in Appendix 23 of the primary analysis CSR. [redacted]

Asia/Japan Subpopulations Results: In subgroup analyses, the hazard ratio for OS favored motesanib over placebo among subjects who were non-white or were from the

"rest of the world" (ie, not from the United States [US], Canada, Australia, or the EU). Ad hoc analyses were performed for subjects (n = 227) who were randomized from Asian countries. Results for the final analysis were consistent with that previously reported in the primary analysis CSR. In the Non-squamous Full Analysis Set (Asia only), median OS time in the motesanib and placebo arms was 21.1 months (95 CI: 15.4, 26.7 months) and 14.9 months (95% CI: 10.8, 18.9 months), respectively. The hazard ratio for OS (motesanib/placebo) was 0.743 (95% CI: 0.547, 1.009) in the stratified Cox proportional hazards model (log-rank p = 0.0564) and 0.710 (95% CI: 0.530, 0.950) in the unstratified Cox proportional hazards model (log-rank p = 0.0206) (Table 14-4.1.96). Median PFS time in the motesanib and placebo arms was 7.0 months (95% CI: 5.8, 7.9 months) and 5.3 months (95% CI: 4.0, 5.7 months), respectively. The hazard ratio for PFS (motesanib/placebo) was 0.577 (95% CI: 0.423, 0.786) in the stratified Cox proportional hazards model (log-rank p = 0.0004) and 0.590 (95% CI: 0.440, 0.790) in the unstratified Cox proportional hazards model (log-rank p = 0.0003) (Table 14-4.2.96).

For the Japan subpopulation (n = 107), median OS time in the motesanib and placebo arms was 25.8 months (95% CI: 16.3, 34.3 months) and 20.7 months (95% CI: 13.5, 27.4 months), respectively. These results are consistent with that previously reported in the primary analysis CSR. The hazard ratio for OS (motesanib/placebo) was 0.944 (95% CI: 0.590, 1.510) in the stratified Cox proportional hazards model (log-rank p = 0.8111) and 0.841 (95% CI: 0.544, 1.301) in the unstratified Cox proportional hazards model (log-rank p = 0.4355) (Table 14-4.1.98). Median PFS time in the motesanib and placebo arms was 7.1 months (95% CI: 6.7, 8.8 months) and 5.8 months (95% CI: 4.2, 7.0 months), respectively. The hazard ratio for PFS (motesanib/placebo) was 0.570 (95% CI: 0.350, 0.928) in the stratified Cox proportional hazards model (log-rank p = 0.0231) and 0.580 (95% CI: 0.369, 0.913) in the unstratified Cox proportional hazards model (log-rank p = 0.0173) (Table 14-4.2.98).

Complete results for the Asia/Japan subpopulations were provided in Appendix 24 of the primary analysis CSR.

Pharmacokinetics Results:

PK analysis was performed at the time of the primary analysis. Limited additional PK data were reported after the primary analysis; therefore, no new PK analysis was performed for this final analysis. Results are reported in the primary analysis CSR.

An additional 35 motesanib and 47 M4 PK samples were received and analyzed for plasma motesanib and M4 concentrations, respectively, after the primary PK analysis was performed. The majority of the 35 motesanib and 47 M4 new PK samples were collected at later timepoints (monotherapy visits) or during unscheduled visits. The values for these samples were consistent with the range of concentrations observed at the time of the primary analysis. The outcome of any queries that were outstanding at the time of the primary analysis did not impact any of the results previously reported.

Patient-Reported Outcomes Results:

Patient-reported outcomes results were provided in the primary analysis CSR. No new analyses related to patient-reported outcomes were performed at the time of the final analysis.

Safety Results:

Exposure data for motesanib at final analysis were similar to exposure data at the time of the primary analysis in the Non-squamous Safety Analysis Set. During the treatment phase, the average daily dose of blinded treatment in the motesanib and placebo arms

was a mean of 121.5 and 131.0 mg, respectively. The total duration of blinded treatment in the motesanib and placebo arms was a mean of 166.1 and 148.9 days, respectively, and subjects were actually administered blinded treatment for a mean of 158.3 and 146.1 days, respectively. The mean cumulative dose of blinded treatment in the motesanib and placebo arms was 19,000.4 and 18,125.2 mg, respectively, for a mean dose intensity of 115.4 and 128.7 mg/day, respectively, and a mean relative dose intensity of 92.3% and 103.0%, respectively (Table 14-3.3.1.1).

The average daily dose of blinded treatment in the motesanib and placebo arms during the monotherapy phase was a mean of 117.8 and 123.7 mg, respectively, and subjects actually received blinded treatment on a mean of 125.8 and 88.7 days, respectively, for a mean cumulative dose of 14,776.6 and 10,949.8 mg, respectively. Dose intensity in the motesanib and placebo arms during the monotherapy phase was a mean of 114.3 and 122.2 mg/day, respectively, for a relative dose intensity of 91.4% and 97.8%, respectively (Table 14-3.3.2.1).

The safety profile of motesanib for the final analysis (Table 3) was consistent with that previously reported in the primary analysis CSR (Table 4) and only minor changes were observed with respect to safety data for all analysis sets. The Non-squamous Safety Analysis Set, at the time of both the primary and final analyses, included 533 subjects who received motesanib and 539 who received placebo.

The Adenocarcinoma Safety Analysis Set included 443 subjects who received motesanib and 434 who received placebo. The overall safety profile in the Adenocarcinoma Safety Analysis Set (Table 14-6.1.2.1) was similar to that of the Non-squamous Safety Analysis Set.

The Squamous Safety Analysis Set included 181 subjects who received motesanib and 173 who received placebo. Safety results of subjects with squamous NSCLC were provided in Appendix 23 of the primary analysis CSR. Safety results at final analysis (Table 14-6.1.4.1) were consistent with those reported in the primary analysis CSR.

Table 3. Final Analysis: Overall Summary of Subject Incidence of Treatment-Emergent Adverse Events (Non-Squamous Safety Analysis Set)

	Placebo (N = 539) n (%)	Motesanib (N = 533) n (%)
All adverse events	521 (97)	512 (96)
Worst grade [a] of 1	43 (8)	20 (4)
Worst grade [a] of 2	158 (29)	100 (19)
Worst grade [a] of 3	189 (35)	200 (38)
Worst grade [a] of 4	75 (14)	112 (21)
Worst grade [a] of 5	56 (10)	80 (15)
Serious adverse events	185 (34)	267 (50)
Worst grade [a] of 1	5 (<1)	2 (<1)
Worst grade [a] of 2	16 (3)	21 (4)
Worst grade [a] of 3	63 (12)	105 (20)
Worst grade [a] of 4	45 (8)	59 (11)
Worst grade [a] of 5	56 (10)	80 (15)
Placebo/Motesanib-related adverse events	285 (53)	387 (73)
Worst grade [a] of 1	89 (17)	53 (10)
Worst grade [a] of 2	101 (19)	118 (22)
Worst grade [a] of 3	65 (12)	160 (30)
Worst grade [a] of 4	22 (4)	45 (8)
Worst grade [a] of 5	8 (1)	11 (2)

[a] Grade is based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 dated December 12, 2003.
[b] Includes all reported fatal adverse events that began within 30 days of last protocol-specified treatment administration.
Treatment-emergent adverse events include adverse events that began between the first administration of protocol-specified treatment and 30 days after the last administration of protocol-specified treatment.
The Non-Squamous Safety Analysis Set includes all subjects who are randomized, receive at least 1 administration of Motesanib or placebo and who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group for which they received therapy.
Events missing relationship are assumed to be related.
Events missing seriousness are assumed to be serious.
Hepatobiliary/pancreatic events indicated as "related to Study Procedures" are assumed to be related to chemotherapy if the subject received Paclitaxel/Carboplatin.

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Table 3. Final Analysis: Overall Summary of Subject Incidence of Treatment-Emergent Adverse Events (Non-Squamous Safety Analysis Set)

	Placebo (N = 539) n (%)	Motesanib (N = 533) n (%)
Serious Placebo/Motesanib-related adverse events	46 (9)	113 (21)
Worst grade [a] of 2	6 (1)	11 (2)
Worst grade [a] of 3	17 (3)	60 (11)
Worst grade [a] of 4	15 (3)	31 (6)
Worst grade [a] of 5	8 (1)	11 (2)
Paclitaxel/Carboplatin-related adverse events	467 (87)	467 (88)
Worst grade [a] of 1	78 (14)	43 (8)
Worst grade [a] of 2	171 (32)	140 (26)
Worst grade [a] of 3	159 (29)	172 (32)
Worst grade [a] of 4	51 (9)	99 (19)
Worst grade [a] of 5	8 (1)	13 (2)
Serious Paclitaxel/Carboplatin-related adverse events	69 (13)	132 (25)
Worst grade [a] of 1	3 (<1)	1 (<1)
Worst grade [a] of 2	9 (2)	9 (2)
Worst grade [a] of 3	26 (5)	61 (11)
Worst grade [a] of 4	23 (4)	48 (9)
Worst grade [a] of 5	8 (1)	13 (2)

[a] Grade is based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 dated December 12, 2003.
[b] Includes all reported fatal adverse events that began within 30 days of last protocol-specified treatment administration.
Treatment-emergent adverse events include adverse events that began between the first administration of protocol-specified treatment and 30 days after the last administration of protocol-specified treatment.
The Non-Squamous Safety Analysis Set includes all subjects who are randomized, receive at least 1 administration of Motesanib or placebo and who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group for which they received therapy.
Events missing relationship are assumed to be related.
Events missing seriousness are assumed to be serious.
Hepatobiliary/pancreatic events indicated as "related to Study Procedures" are assumed to be related to chemotherapy if the subject received Paclitaxel/Carboplatin.

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Table 3. Final Analysis: Overall Summary of Subject Incidence of Treatment-Emergent Adverse Events (Non-Squamous Safety Analysis Set)

	Placebo (N = 539) n (%)	Motesanib (N = 533) n (%)
Discontinuation of Placebo/Motesanib due to adverse event	78 (14)	166 (31)
Not serious	28 (5)	81 (15)
Serious	50 (9)	85 (16)
Discontinuation of Paclitaxel/Carboplatin due to adverse event	76 (14)	110 (21)
Not serious	42 (8)	64 (12)
Serious	34 (6)	46 (9)
Fatal adverse events on study [b]	56 (10)	80 (15)
Serious	56 (10)	80 (15)

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[a] Grade is based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 dated December 12, 2003.
[b] Includes all reported fatal adverse events that began within 30 days of last protocol-specified treatment administration.
Treatment-emergent adverse events include adverse events that began between the first administration of protocol-specified treatment and 30 days after the last administration of protocol-specified treatment.
The Non-Squamous Safety Analysis Set includes all subjects who are randomized, receive at least 1 administration of Motesanib or placebo and who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group for which they received therapy.
Events missing relationship are assumed to be related.
Events missing seriousness are assumed to be serious.
Hepatobiliary/pancreatic events indicated as "related to Study Procedures" are assumed to be related to chemotherapy if the subject received Paclitaxel/Carboplatin.

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Table 4. Primary Analysis: Overall Summary of Subject Incidence of Treatment-emergent Adverse Events (Non-squamous Safety Analysis Set)

	Placebo (N = 539) n (%)	Motesanib (N = 533) n (%)
All adverse events	520 (96)	512 (96)
Worst grade [a] of 1	43 (8)	22 (4)
Worst grade [a] of 2	158 (29)	102 (19)
Worst grade [a] of 3	192 (36)	201 (38)
Worst grade [a] of 4	77 (14)	113 (21)
Worst grade [a] of 5	50 (9)	74 (14)
Serious adverse events	184 (34)	261 (49)
Worst grade [a] of 1	5 (<1)	2 (<1)
Worst grade [a] of 2	17 (3)	20 (4)
Worst grade [a] of 3	64 (12)	105 (20)
Worst grade [a] of 4	47 (9)	60 (11)
Worst grade [a] of 5	50 (9)	74 (14)
Missing grade	1 (<1)	0 (0)
Placebo/Motesanib-related adverse events	284 (53)	387 (73)
Worst grade [a] of 1	89 (17)	53 (10)
Worst grade [a] of 2	101 (19)	119 (22)
Worst grade [a] of 3	64 (12)	159 (30)
Worst grade [a] of 4	22 (4)	45 (8)
Worst grade [a] of 5	8 (1)	11 (2)

[a] Grade is based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 dated December 12, 2003.
[b] Includes all reported fatal adverse events that began within 30 days of last protocol-specified treatment administration.
Treatment-emergent adverse events include adverse events that began between the first administration of protocol-specified treatment and 30 days after the last administration of protocol-specified treatment.
The Non-squamous Safety Analysis Set includes all subjects who are randomized, receive at least 1 administration of Motesanib or placebo and who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group for which they received therapy.
Events missing relationship are assumed to be related.
Events missing seriousness are assumed to be serious.
Hepatobiliary/pancreatic events indicated as "related to Study Procedures" are assumed to be related to chemotherapy if the subject received Paclitaxel/Carboplatin.

Program: /stat/amg706/onc/20050201/analysis/csr_2011/tables/t-ae-summary.sas
Output: t14-06-001-001-001-ae-summary-nssaf-p.rtf (Date Generated: 25MAR11:12:53:56) Source Data: demo, ae

Table 4. Primary Analysis: Overall Summary of Subject Incidence of Treatment-emergent Adverse Events (Non-squamous Safety Analysis Set)

	Placebo (N = 539) n (%)	Motesanib (N = 533) n (%)
Serious Placebo/Motesanib-related adverse events	46 (9)	113 (21)
Worst grade [a] of 2	6 (1)	11 (2)
Worst grade [a] of 3	17 (3)	60 (11)
Worst grade [a] of 4	15 (3)	31 (6)
Worst grade [a] of 5	8 (1)	11 (2)
Paclitaxel/Carboplatin-related adverse events	467 (87)	469 (88)
Worst grade [a] of 1	78 (14)	43 (8)
Worst grade [a] of 2	171 (32)	137 (26)
Worst grade [a] of 3	159 (29)	175 (33)
Worst grade [a] of 4	51 (9)	101 (19)
Worst grade [a] of 5	8 (1)	13 (2)
Serious Paclitaxel/Carboplatin-related adverse events	69 (13)	134 (25)
Worst grade [a] of 1	3 (<1)	1 (<1)
Worst grade [a] of 2	9 (2)	8 (2)
Worst grade [a] of 3	26 (5)	62 (12)
Worst grade [a] of 4	23 (4)	50 (9)
Worst grade [a] of 5	8 (1)	13 (2)

[a] Grade is based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 dated December 12, 2003.
[b] Includes all reported fatal adverse events that began within 30 days of last protocol-specified treatment administration.
Treatment-emergent adverse events include adverse events that began between the first administration of protocol-specified treatment and 30 days after the last administration of protocol-specified treatment.
The Non-squamous Safety Analysis Set includes all subjects who are randomized, receive at least 1 administration of Motesanib or placebo and who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group for which they received therapy.
Events missing relationship are assumed to be related.
Events missing seriousness are assumed to be serious.
Hepatobiliary/pancreatic events indicated as "related to Study Procedures" are assumed to be related to chemotherapy if the subject received Paclitaxel/Carboplatin.

Program: /stat/amg706/onc/20050201/analysis/csr_2011/tables/t-ae-summary.sas
Output: t14-06-001-001-001-ae-summary-nssaf-p.rtf (Date Generated: 25MAR11:12:53:56) Source Data: demo, ae

Table 4. Primary Analysis: Overall Summary of Subject Incidence of Treatment-emergent Adverse Events (Non-squamous Safety Analysis Set)

	Placebo (N = 539) n (%)	Motesanib (N = 533) n (%)
Discontinuation of Placebo/Motesanib due to adverse event	80 (15)	165 (31)
Not serious	28 (5)	80 (15)
Serious	52 (10)	85 (16)
Discontinuation of Paclitaxel/Carboplatin due to adverse event	77 (14)	110 (21)
Not serious	42 (8)	64 (12)
Serious	35 (6)	46 (9)
Fatal adverse events on study [b]	50 (9)	74 (14)
Serious	50 (9)	74 (14)

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[a] Grade is based on the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 dated December 12, 2003.
[b] Includes all reported fatal adverse events that began within 30 days of last protocol-specified treatment administration.
Treatment-emergent adverse events include adverse events that began between the first administration of protocol-specified treatment and 30 days after the last administration of protocol-specified treatment.
The Non-squamous Safety Analysis Set includes all subjects who are randomized, receive at least 1 administration of Motesanib or placebo and who have non-squamous histology, as recorded on the CRF at baseline. Subjects are included in the treatment group for which they received therapy.
Events missing relationship are assumed to be related.
Events missing seriousness are assumed to be serious.
Hepatobiliary/pancreatic events indicated as "related to Study Procedures" are assumed to be related to chemotherapy if the subject received Paclitaxel/Carboplatin.

Program: /stat/amg706/onc/20050201/analysis/csr_2011/tables/t-ae-summary.sas
Output: t14-06-001-001-001-ae-summary-nssaf-p.rtf (Date Generated: 25MAR11:12:53:56) Source Data: demo, ae

In the final analysis, treatment-emergent adverse events were reported for 96% and 97% of subjects in the motesanib and placebo treatment arms, respectively (Table 5). Differences of ≥ 5% were noted between the treatment arms in the subject incidence of adverse events (all were higher in the motesanib arm) with the following preferred terms (motesanib vs placebo, respectively): diarrhea (48% vs 22%), nausea (42% vs 33%), decreased appetite (35% vs 27%), vomiting (33% vs 26%), fatigue (33% vs 28%), neutropenia (28% vs 20%), hypertension (26% vs 6%), thrombocytopenia (21% vs 15%), rash (18% vs 11%), weight decreased (17% vs 9%), abdominal pain (17% vs 6%), headache (16% vs 9%), stomatitis (11% vs 5%), proteinuria (9% vs 3%), and aspartate aminotransferase increased (7% vs 2%) (Table 14-6.12.9.3).

Table 5. Subject Incidence of Treatment-emergent Adverse Events by Preferred Term Occurring in ≥ 20% of Subjects in the Motesanib Arm in Descending Order of Frequency (Non-squamous Safety Analysis Set)

Preferred Term	Placebo (N = 539) n (%)	Motesanib (N = 533) n (%)
Number of subjects reporting adverse events	521 (97)	512 (96)
Diarrhoea	118 (22)	256 (48)
Alopecia	236 (44)	245 (46)
Nausea	176 (33)	222 (42)
Decreased appetite	147 (27)	186 (35)
Vomiting	142 (26)	178 (33)
Fatigue	151 (28)	177 (33)
Neutropenia	110 (20)	149 (28)
Hypertension	35 (6)	139 (26)
Anaemia	136 (25)	129 (24)
Neuropathy peripheral	111 (21)	129 (24)
Constipation	131 (24)	118 (22)
Thrombocytopenia	83 (15)	112 (21)
Arthralgia	98 (18)	111 (21)

Source: Table 14-6.12.1.1

The subject incidence of grade of 3, 4, or 5 adverse events was 74% in motesanib-treated subjects and 59% in placebo-treated subjects (Table 14-6.12.10.1). Differences of ≥ 5% were noted between the treatment arms in the subject incidence of grade 3, 4, or 5 adverse events (all were higher in the motesanib arm) in the following preferred terms (motesanib vs placebo, respectively): neutropenia (22% vs 15%), diarrhea (9% vs 1%), and hypertension (7% vs 1%) (Table 14-6.12.11.1).

Serious adverse events were reported in 50% of subjects treated with motesanib and 34% of subjects treated with placebo (Table 14-6.4.1). A ≥ 5% difference in the subject incidence of serious adverse events was noted between the treatment arms for the preferred term of diarrhea (6% motesanib vs 1% placebo) (Table 14-6.12.9.5).

Fatal adverse events occurring on study (ie, within 30 days of the last dose of study treatment) were reported for 15% of subjects treated with motesanib and 10% of subjects treated with placebo (Table 14-6.12.2.1). Preferred terms reported in more motesanib-treated subjects than in placebo-treated subjects (difference of ≥ 3 subjects) were (motesanib vs placebo): pneumonia (7 vs 0), general physical health deterioration (6 vs 1), respiratory failure (5 vs 2), hemoptysis (3 vs 0), and metastases to central nervous system (3 vs 0). In several of these subjects, medical histories and comorbid conditions were present as contributing factors to the fatal adverse events. Fewer subjects treated with motesanib than subjects treated with placebo had fatal adverse events for the following preferred terms (motesanib vs placebo): pulmonary embolism (3 vs 6) and cardio-respiratory arrest (2 vs 4).

Overall, 31% and 14% of subjects treated with motesanib and placebo, respectively, had adverse events leading to discontinuation of investigational product (Table 14-6.8.1).

The most frequently reported (≥ 1%) events leading to discontinuation of investigational product in the motesanib arm (motesanib vs placebo, respectively) were diarrhea (3% vs < 1%), cholecystitis (2% vs < 1%), abdominal pain (1% vs 0%), hemoptysis (1% vs < 1%), asthenia (1% vs < 1%), and neutropenia (1% vs 0%) (Table 14-6.8.1.4). The subject incidence of adverse events leading to discontinuation of chemotherapy (carboplatin and/or paclitaxel) was higher in the motesanib arm compared with the placebo arm (21% vs 14%). The most frequently reported (≥ 1%) events leading to discontinuation of chemotherapy in the motesanib arm (motesanib vs placebo, respectively) were peripheral sensory neuropathy (2% vs < 1%), peripheral neuropathy (2% vs 1%), thrombocytopenia (2% vs 2%), neutropenia (1% vs < 1%), and fatigue (1% vs < 1%) (Table 14-6.9.1.4).

Treatment-emergent EOIs (non-infectious diarrhea, hypertension, reversible posterior leukoencephalopathy syndrome events, gallbladder related disorders, arterial thromboembolic events, venous thromboembolic events, cardiac failure, cardiomyopathy, hypothyroidism, hemorrhage events, gastrointestinal perforation, proteinuria, impaired wound healing, acute pancreatitis, drug related hepatic disorders, hematopoietic cytopenias, embolic and thrombotic events, vessel type unspecified and mixed arterial and venous, and peripheral neuropathy) were reported for 92% of subjects treated with motesanib and 90% of subjects treated with placebo (Table 14-6.6.1).

The incidence of events was ≥ 5% higher in the motesanib arm compared with the placebo arm in the following EOIs: non-infectious diarrhea (48% vs 23%), hypertension (27% vs 6%), gallbladder related disorders (8% vs <1%), hypothyroidism (7% vs 2%), hemorrhage terms (23% vs 16%), proteinuria (10% vs 4%), drug related hepatic disorders (14% vs 7%), hematopoietic cytopenias (52% vs 45%), peripheral neuropathy (53% vs 48%), and reversible posterior leukoencephalopathy syndrome (16% vs 8%) (Table 14-6.6.1.4).

While the incidence of preferred terms retrieved using the broad search strategy for acute pancreatitis was higher in the motesanib arm compared to placebo (58% vs 47%, respectively), many of the terms retrieved were nonspecific (nausea, vomiting, abdominal pain, etc). The incidence of preferred terms retrieved using the narrow search strategy for acute pancreatitis was similar for both treatment groups (<1% for both) (primary analysis CSR Table 14-6.6.1.11).

Using a pre-specified case definition, 1 motesanib-treated subject had a confirmed reversible posterior leukoencephalopathy event compared with none in the placebo arm. The subject incidences for all other EOIs were generally similar across treatment arms.

Adverse events known to be associated with carboplatin administration were also reviewed. The subject incidence of adverse events of neutropenia and thrombocytopenia, as well as the subject incidence of nausea and vomiting, was higher in the motesanib arm compared with placebo. The subject incidence of grade 3 and 4 neutropenia and thrombocytopenia laboratory abnormalities, however, was similar between the 2 arms.

In general, changes in laboratory values were consistent with results observed in previous motesanib studies (motesanib diphosphate Investigator's Brochure).

The changes observed in systolic and diastolic blood pressure were consistent with the more frequent reports of hypertension in subjects treated with motesanib when compared to subjects treated with placebo or bevacizumab.

Asia/Japan Subpopulations Results:

Full results for the Asian/Japan subpopulations were provided in Appendix 24 of the primary analysis CSR. Results at final analysis were very similar to those at the time of primary analysis.

Ad hoc summaries were provided for subjects who were randomized from Asian countries. The Non-squamous Safety Analysis Set (Asia only) included 108 subjects who received motesanib and 114 subjects who received placebo. Mean number of days of exposure to investigational product during the treatment phase was 211.4 and 148.9 days in the motesanib and placebo arms, respectively, with a mean relative dose intensity of 90.4% for the motesanib arm and 96.9% in placebo arm (Table 14-3.3.1.96).

Treatment-emergent adverse events were reported for 100% of subjects in the motesanib arm and 99% of subjects in the placebo arm (Table 14-6.1.1.96). A complete summary of adverse events with ≥ 5% differences noted between the treatment arms was provided in Appendix 24 of the primary analysis CSR.

The subject incidence of grade of 3, 4, or 5 adverse events was 79% in motesanib-treated subjects and 61% in placebo-treated subjects (Table 14-6.17.1.96). Differences of ≥ 5% were noted between the treatment arms in the following preferred terms (motesanib vs placebo, respectively): neutropenia (36% vs 22%), hypertension (13% vs 3%), thrombocytopenia (11% vs 4%), diarrhea (6% vs 0%), vomiting (6% vs 0%) and fatigue (6% vs < 1%).

Serious adverse events were reported in 35% of subjects treated with motesanib and 34% of subjects treated with placebo (Table 14-6.4.96). No difference ≥ 5% was noted between the treatment arms for any serious adverse event.

Fatal adverse events (occurring within 30 days of the last dose of protocol-specified treatment) were reported for 5% of subjects in the motesanib arm and 4% of subjects in the placebo arm (Table 14-6.12.2.96). No notable differences between treatment arms in the number of subjects with fatal adverse events were observed.

Overall, 26% and 9% of subjects treated with motesanib and placebo, respectively, had adverse events leading to discontinuation of investigational product (Table 14-6.12.6.96). The most frequently reported (≥ 1%) events leading to discontinuation of investigational product in the motesanib arm (motesanib vs placebo, respectively) were cholecystitis (3% vs 2%) and abdominal pain, increased alanine aminotransferase, hypertension, neutropenia, and pneumonia (2% vs 0% each). The subject incidence of adverse events leading to discontinuation of chemotherapy (carboplatin and/or paclitaxel) was 15% in the motesanib arm and 11% in the placebo arm (Table 14-6.12.5.96). The most frequently reported (≥ 1%) events leading to discontinuation of chemotherapy (motesanib vs placebo, respectively) were thrombocytopenia (2% vs 2%), peripheral sensory neuropathy (2% vs < 1%), pneumonia (2% vs < 1%), neutropenia (2% vs 0%), septic shock (< 1% vs 3%), and peripheral neuropathy (< 1% vs 2%).

Treatment-emergent EOIs (non-infectious diarrhea, hypertension, reversible posterior leukoencephalopathy syndrome events, gallbladder related disorders, arterial thromboembolic events, venous thromboembolic events, cardiac failure, cardiomyopathy, hypothyroidism, hemorrhage events, gastrointestinal perforation, proteinuria, impaired wound healing, acute pancreatitis, drug related hepatic disorders, hematopoietic cytopenias, embolic and thrombotic events, vessel type unspecified and mixed arterial and venous, and peripheral neuropathy) were reported for 99% of subjects treated with motesanib and 96% of subjects treated with placebo (Table 14-6.6.96).

The incidence of events was ≥ 5% higher in the motesanib arm compared with the placebo arm for the following EOIs (motesanib vs placebo): peripheral neuropathy (84% vs 65%), non-infectious diarrhea (64% vs 33%), hypertension (51% vs 9%), drug-related hepatic disorders (25% vs 10%), proteinuria (16% vs 2%), reversible posterior leunoencephalopathy syndrome (11% vs 3%), hypothyroidism (9% vs 2%), and gallbladder related disorders (9% vs 2%) (Table 14-6.6.96).

While the incidence of preferred terms retrieved using the broad search strategy for acute pancreatitis was higher in the motesanib arm compared to placebo (77% vs 58%, respectively), many of the terms retrieved were nonspecific (nausea, vomiting, abdominal pain, etc) and did not represent true cases of pancreatitis. Using the narrow search strategy, consistent with that of the primary analysis, acute pancreatitis was reported for 1 subject in the placebo arm and none in the motesanib arm.

Using a pre-specified case definition, consistent with that of the primary analysis, 1 motesanib-treated subject had a confirmed reversible posterior leukoencephalopathy event compared with none in the placebo arm.

In general, changes in laboratory values were consistent with results observed in previous motesanib studies (motesanib diphosphate Investigator's Brochure).

Japan Subpopulation

Safety analyses for the Japan subpopulation were performed at the time of the primary analysis. No new analysis was performed for the final analysis.

Conclusions:

This final analysis CSR updates the previous primary analysis CSR with additional efficacy and safety data collected through study completion. Overall results were very similar to those in the primary analysis.

The addition of motesanib to combination chemotherapy with paclitaxel and carboplatin did not increase OS significantly compared with the addition of placebo, either among subjects with non-squamous NSCLC or in the subgroup of subjects with adenocarcinoma as shown at the time of primary analysis and at final analysis.

Limited additional PK data were reported after the primary analysis; therefore, no new PK analysis was performed for this final analysis. The additional data were consistent with the data obtained previously for the primary analysis. The trough level of M4 was higher than the motesanib level in subjects with non-squamous NSCLC. Coadministration of motesanib with carboplatin appears to slightly increase the total and unbound plasma concentration of carboplatin.

The safety profile of motesanib for the final analysis was consistent with that previously reported in the primary analysis report. The Final Analysis results showed no shifts in data that would change the conclusions described in the primary analysis CSR.