2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 386

Name of Active Ingredient: AMG 386

Title of Study: A Phase 2, Randomized, Double-Blind, Placebo Controlled Study of AMG 386 in Combination with FOLFIRI in Subjects with Previously Treated Metastatic Colorectal Carcinoma

Investigator(s) and Study Center(s): This study was conducted at 38 sites in the United States, Europe, Russia, India, and Australia. Names and addresses of principal investigators are listed in Appendix 4.

Publication(s): None as of the date of this report

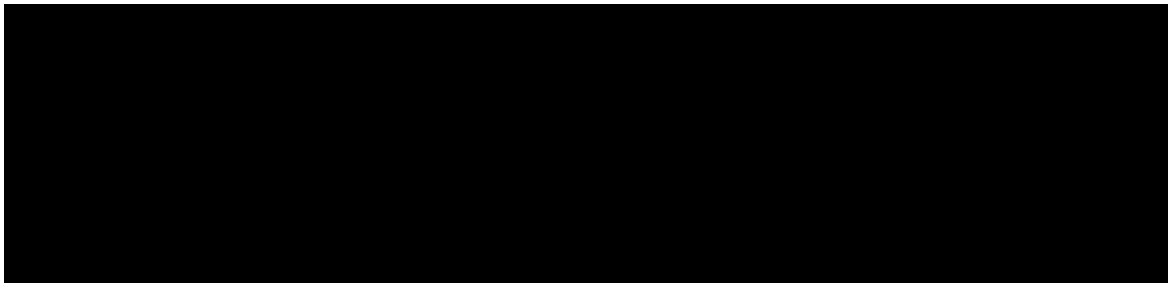
Study Period: 05 December 2008 (date first subject enrolled) to 09 July 2010 (primary analysis data cutoff date)

Development Phase: 2

Introduction and Objectives: AMG 386 is a first-in-class antiangiogenic investigational product that provides potent and selective inhibition of angiopoietins. AMG 386 inhibits angiogenesis by sequestering angiopoietin-1 and -2 (Ang1 and Ang2), thereby preventing their interaction with the tyrosine kinase receptor with immunoglobulin and epidermal growth factor homology domain 2 (Tie2). This study was designed to evaluate the activity of AMG 386 as a second-line treatment in subjects with metastatic colorectal cancer.

The primary objective of this phase 2, randomized, double-blind, placebo-controlled study was to estimate the treatment effect as measured by progression-free survival (PFS) of subjects receiving AMG 386 and 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) combination regimen compared with FOLFIRI and placebo.

The secondary objectives were to evaluate other measures of treatment effect (objective response rate, duration of response, overall survival); to estimate PFS and other measures of efficacy by Kirsten rat sarcoma-2 virus *(KRAS)* status, to evaluate the relative dose intensity of AMG 386 and all FOLFIRI components; to evaluate the pharmacokinetics of AMG 386 (all subjects) and FOLFIRI components (subgroup of subjects at selected sites outside of Europe), to estimate the immunogenicity as assessed by the incidence of anti-AMG 386 antibody formation; to estimate the impact of AMG 386 on cancer-related symptoms based on patient-reported outcomes (PRO) using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30); and to evaluate the safety and tolerability of the combination regimen of AMG 386 with FOLFIRI.



Methodology: This phase 2, randomized, placebo-controlled, multicenter study was designed to estimate the treatment effect of PFS and to evaluate the safety and tolerability of AMG 386 in combination with FOLFIRI compared with FOLFIRI/placebo as a second line treatment of subjects with metastatic colorectal cancer. Approximately 138 subjects were to be randomized 2:1 to one of the following treatment arms:

- Arm A: AMG 386 10 mg/kg IV once weekly (QW), FOLFIRI once every 2 weeks (Q2W)
- Arm B: AMG 386 placebo IV QW, FOLFIRI Q2W

The FOLFIRI regimen consisted of the following: irinotecan 180 mg/m^2 IV over 90 (± 15) minutes on day 1, leucovorin 400 mg/m^2 IV over 2 hours on day 1, 5-FU 400 mg/m^2 IV bolus, followed by 2400 mg/m^2 continuous IV infusion over 46 (± 2) hours.

Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1). Upon randomization, the subject received the first dose of FOLFIRI and AMG 386 or placebo within 7 days. AMG 386 was administered on day 1 of week 1 prior to FOLFIRI chemotherapy. Subjects received study treatment until radiographic disease progression per Response Evaluation Criteria in Solid Tumor (RECIST v 1.0) with modifications (Appendix 1), clinical progression, unacceptable toxicity, subject withdrawal of consent, or death. Subjects who discontinued study treatment for any reason other than death completed a safety follow up visit no less than 30 days and no more than 37 days from the last dose of study medication.

Radiological imaging to assess disease status and progression was performed every 8 weeks ± 1 week during the study until disease progression, initiation of a new treatment or full withdrawal of consent. In addition, any subject who discontinued study treatment prior to disease progression continued to have radiological imaging performed every 8 weeks ± 1 week during the long term follow-up period until disease progression, initiation of a new treatment, or full withdrawal of consent.

Subjects alive at the time of discontinuation of all study medications were followed for up to 30 months from the date the last subject was randomized to determine overall survival.

Number of Subjects Planned: Approximately 138 subjects

Number of Subjects Enrolled: 144

Sex: 60 (42%) women and 84 (58%) men

Age: mean (standard deviation [SD]) was 55.2 (12.6) years (range 23 to 79)

Ethnicity (Race): 110 (76%) white or Caucasian, 2 (1%) black or African American, and 32 (22%) Asian

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men or women ≥ 18 years of age with histologically confirmed adenocarcinoma of the colon or rectum with metastatic disease and an ECOG performance status of 0 or 1. Subjects with progressive disease after 1 prior chemotherapy regimen for metastatic disease that consisted of the combination of a fluoropyrimidine-based chemotherapy and an oxaliplatin-based chemotherapy were eligible. Subjects must have had radiographically documented disease progression per RECIST v 1.0 with modifications either while receiving or ≤ 6 months after the last dose of prior chemotherapy regimen. Subjects had at least 1 uni-dimensionally measured lesion per RECIST v 1.0 with modifications criteria and all sites of disease were evaluated ≤ 28 days before randomization. Subjects were required to have adequate organ and hematological function and a life expectancy of ≥ 3 months. For establishing *KRAS* status, subjects were required to have a formalin-fixed paraffin-embedded tumor block or an unstained tumor block of the primary tumor or of a metastatic lesion. Full inclusion and exclusion criteria are provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 386 or placebo were administered IV once weekly; AMG 386 was administered at a dose of 10 mg/kg. The manufacturing batch numbers of AMG 386 administered in this study were [redacted]. The manufacturing batch numbers of placebo administered in this study were [redacted]

Duration of Treatment: Subjects received study treatment until radiographic disease progression, clinical progression, unacceptable toxicity, subject withdrawal of consent or death. The estimated median duration of treatment was 4 months for subjects receiving FOLFIRI/AMG 386 placebo (Arm B) and 5.8 months for subjects receiving FOLFIRI/AMG 386 (Arm A).

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: All subjects received FOLFIRI regimen (Q2W) which consisted of irinotecan 180 mg/m^2 IV, leucovorin 400 mg/m^2 IV, and 5-FU 400 mg/m^2 IV bolus, followed by 2400 mg/m^2 continuous IV infusion. Chemotherapy agents were obtained from commercial sources.

Study Endpoints

The primary endpoint was PFS, defined as the time from randomization date to date of disease progression or death.

Secondary endpoints included the following:

- objective response rate (ORR): the incidence of either confirmed complete response (CR) or confirmed partial response (PR) per RECIST v 1.0 with modifications
- duration of response (DOR): time from first confirmed objective response to disease progression (per RECIST v 1.0 with modifications) or death (only calculated for those subjects who respond)
- overall survival (OS): time from date of randomization to date of death from any cause
- PFS by KRAS status
- incidence of adverse events and significant laboratory changes from baseline
- overall exposure, dose adjustments and rates of discontinuation for FOLFIRI
- pharmacokinetic parameters (maximum observed serum concentration [C_{max}] and area under the curve [AUC]) of AMG 386
- pharmacokinetic parameters of FOLFIRI (5-FU: concentration at steady state [C_{ss}] and AUC; irinotecan and its active metabolite SN-38: C_{max} and AUC) in a subgroup of subjects in selected sites outside of Europe
- incidence of anti-AMG 386 antibody formation
- change in tumor burden as measured by sums of the longest diameter of target lesions
- time to response (TTR): time from randomization date to date of first response for confirmed responders
- time to progression (TTP): time from date of randomization to date of disease progression per RECIST v 1.0 with modifications
- change in PRO as assessed with the EORTC QLQ-C30

Statistical Methods: The goal of the primary statistical analysis was to estimate the treatment effect on PFS on AMG 386 in combination with FOLFIRI compared with FOLFIRI in combination with placebo in subjects with metastatic colorectal cancer. The primary analysis was event-driven and was planned to occur when 100 PFS events were observed. PFS was based upon investigator assessments of disease progression. The primary analysis of PFS was conducted in the intention-to-treat (ITT) analysis set. Hazard ratios and 2-sided 80% confidence intervals were calculated using Cox regression models stratified by the randomization factor (ECOG status of 0 or 1). Kaplan-Meier (K-M) curves and K-M medians, if estimable, were provided. Analyses of OS were performed as for PFS. Analyses of ORR, DOR, and TTR were conducted in the ITT analysis set.

Safety assessments, including analyses of treatment-emergent adverse events; changes in laboratory values, electrocardiogram parameters, and vital signs; and the incidence of anti-AMG 386 antibody formation, were provided for all randomized subjects who received at least 1 dose of study drug.

PRO analyses were to be performed for subjects in the ITT analysis set with at least 1 PRO assessment prior to disease progression. Subject completion rates, dropout patterns, and PRO scores at each time point, including change from baseline, were to be summarized. Descriptive summaries on observed data were provided for each of the scale scores for the QLQ-C30 and FCSI at each assessed time point. A mixed effects model for all PRO endpoints was performed.

AMG 386, 5-FU and irinotecan (and its active metabolite SN-38) individual serum concentrations and summary statistics for each dose group were provided.

Summary of Results:

Subject Disposition: Of 187 subjects screened, a total of 144 subjects were randomized to receive AMG 386 (10 mg/kg IV QW) and FOLFIRI (Arm A) or placebo (IV QW) and FOLFIRI (Arm B). Ninety-four (99%) subjects randomized to the AMG 386 treatment group and 49 (100%) subjects in the placebo treatment group received at least 1 dose of study drug. At the time of the primary analysis data cutoff, 15 (16%) subjects in the AMG 386 treatment group and 12 (24%) subjects in the placebo group were continuing treatment with at least 1 of the study drugs. One hundred seventeen (81%) subjects had ended treatment with AMG 386 or placebo, and 116 (81%) subjects had ended FOLFIRI treatment.

Disease progression was the most common reason for discontinuation of investigational product (62% and 55%, in the AMG 386 and placebo treatment groups, respectively), and was also the most common reason for discontinuation of FOLFIRI (61% and 53%, respectively). More subjects in the AMG 386 treatment group discontinued investigational product due to an adverse event (12% compared with 4% in the placebo treatment group). The proportion of subjects discontinuing FOLFIRI due to an adverse event was comparable between the treatment groups (9% and 8%, respectively).

The proportion of subjects with *KRAS* wildtype, mutant, or unknown (ie, unevaluable tumor specimen) status was 53%, 33%, and 14%, respectively. Fewer subjects in the AMG 386 treatment group had the wildtype *KRAS* phenotype compared with the placebo treatment group (49% and 59%, respectively), while more subjects had a mutant *KRAS* phenotype (36% and 29%, respectively). *KRAS* status was not evaluable for 15% and 12% of subjects in the AMG 386 and placebo treatment groups who had a tumor specimen available for assessment.

Efficacy Results: In the ITT population, the estimated hazard ratio (80% confidence interval [CI]) for a PFS event in the AMG 386 group relative to placebo was 1.231 (0.939, 1.612), p-value = 0.325 (median PFS of 3.5 and 5.2 months, in the AMG 386 and placebo groups, respectively). ORR (80% CI) was 14.3% (9.5, 20.4) for the AMG 386 treatment group compared with 0% (0, 5.0) for those subjects in the placebo group. Median DOR (80% CI) for the responders, all in the AMG 386 treatment group, was 6.2 (5.6, 7.4) months. Median OS was 11.9 months and 8.8 months for subjects in the AMG 386 and placebo treatment groups, respectively (hazard ratio [80% CI] = 0.901 [0.635, 1.279], p-value = 0.703).

An assessment of PFS by *KRAS* mutation status was a secondary endpoint. For subjects in the mutant *KRAS* subgroup, the median PFS was 2.8 and 5.5 months in the AMG 386 and placebo groups, respectively (hazard ratio = 2.094, 80% CI = 1.149 to 3.817; p-value = 0.115). For subjects in the wildtype *KRAS* subgroup, the median PFS was 5.2 months and 4.5 months in the respective treatment groups (hazard ratio = 0.962, 80% CI = 0.672 to 1.376; p-value = 0.890).

Pharmacokinetic Results: The median (% CV) AMG 386 C_{max} and minimum observed serum concentration (C_{min}) steady state values in subjects with metastatic colorectal carcinoma following co-administration of FOLFIRI were 221 (69.8%) and 15.6 (56.2%) µg/mL at Week 5, which are similar to the values observed in the first-in-human (FIH) study (20040169). The AUC_{ss} on Week 5, estimated from limited subset of patients (n=7), has a mean (% CV) value lower than that of the FIH study (6.07 [26%] compared with 9.90 [61%] mg*hr/mL). Median (%CV) irinotecan C_{max} values at Week 5 appeared to be similar in placebo and AMG 386-treated subjects (1970 [37.9%] ng/mL compared with 1800 [54.7%] ng/mL), respectively, which are comparable to those of literature values (Langenberg et al, 2010). The 5-FU exposure in general was higher in females than in males, which is also consistent with the literature (Kubota, 2003; Yamashita et al, 2002; Milano et al, 1992). The median values of SN-38 C_{max} and 5-FU C_{ss} (all data) were lower in the AMG 386-treated subjects compared to placebo-treated subjects (approximately 30% and 40%, respectively). However, the variability was high, such that statistical difference was not supported. Nonetheless, the C_{max} of SN-38 in the AMG 386 dose arm from the intensive PK subset was comparable to those values reported in the literature (Langenberg et al, 2010).

Based on the population pharmacokinetics analysis, baseline creatinine clearance (CrCl) was found to be a significant covariate for AMG 386 serum clearance (CL). The median AUC_{SS} value for AMG 386 at a dose of 10 mg/kg (n = 94) was 7.9 mg•hr/mL.

Antibody Results: Preexisting, non-neutralizing antibodies were observed in 3 of 90 subjects (3.3%) in the AMG 386 treatment group. Non-neutralizing, anti-AMG 386 binding antibodies developed postbaseline in 1 of 85 subjects (1.2%) in the AMG 386 treatment group. No subject tested positive for neutralizing antibodies during the study.

Patient-reported Outcome Results: Responses to the QLQ-C30 instrument were analyzed for 97% and 100% of subjects in the 10-mg/kg and placebo groups, respectively, and for the FCSI instrument, responses were analyzed for 97% and 98% of subjects, respectively. In an analysis using a linear mixed model, the differences between the treatment groups in the least squares (LS)-adjusted mean change from baseline scores through week 21 were small and were not statistically significant for all QLQ-C30 and FCSI scores. Sensitivity analyses using pattern-mixture models were generally consistent with the linear mixed model results except for the QLQ-C30 social functioning scale in the early dropout group, which had a difference between the treatment groups in the LS-adjusted mean change from baseline scores of -18.1 and 3.5 for the early dropout and late dropout groups, respectively.

[redacted].

Safety Results: The overall subject incidence of adverse events was similar between the AMG 386 and placebo groups (97% and 98% in the AMG 386 and placebo groups, respectively). Grade 3 and higher adverse events occurred in 62% and 65% of subjects in the respective treatment groups; the overall severity of adverse events was similar (within 5 percentage points) or lower in the AMG 386 group compared with placebo (grade 3: 44%, 39% in AMG 386 and placebo groups, respectively; grade 4: 12%, 20%, and grade 5: 6%, 6%). Adverse events were reported as related to treatment with AMG 386 (or placebo) for 35% and 33% of subjects in the AMG 386 and placebo treatment groups, respectively, and to FOLFIRI treatment for 88% and 90% of subjects, respectively. Adverse events led to discontinuation from the treatment phase (ie, investigational product or FOLFIRI treatment) or study for 12% of subjects in both the AMG 386 and placebo groups.

In general, the incidence of adverse events by Medical Dictionary for Regulatory Activities (MedDRA) preferred term was similar between the AMG 386 and placebo treatment groups. The most common adverse events occurring in ≥ 10% subjects in either treatment group were diarrhea (AMG 386: 47%, placebo: 41%), nausea (44%, 37%), neutropenia (41%, 57%), asthenia (31%, 33%), decreased appetite (28%, 16%), alopecia (26%, 37%), fatigue (24%, 18%), constipation (21%, 18%), peripheral edema (20%, 4%), vomiting (17%, 39%), abdominal pain (14%, 10%), pyrexia (14%, 8%), leucopenia (13%, 12%), stomatitis (13%, 8%), cough (7%, 14%), and anemia (6%, 24%).

Serious adverse events were reported for 28% and 33% of subjects in the AMG 386 and placebo groups, respectively. The most frequently reported serious adverse events (ie, occurring in ≥ 5% subjects either treatment group) by preferred term (AMG 386 and placebo) were febrile neutropenia (2%, 6%), neutropenia (1%, 6%), abdominal pain (0%, 6%), and vomiting (0%, 6%). Treatment-related serious adverse events were reported for 16% of subjects in the AMG 386 group and 24% of subjects in the placebo treatment group.

Edema is an identified risk with AMG 386 administration. Edema adverse events were reported for 26% of subjects in the AMG 386 treatment group and 6% of subjects in the placebo treatment group, with 1 event of grade 3 or higher (lymphoedema, AMG 386 treatment group). The most common edema adverse event was peripheral edema (AMG 386: 20%, placebo: 4%). The subject incidence of other adverse events of interest and potential risks (arterial and venous thromboembolic events, cardiac toxicity, gastrointestinal perforation, hemorrhage, hematologic toxicity, hypertension, hypothyroidism, impaired wound healing, pancreatic toxicity, proteinuria, hypokalemia and infusion reactions) was similar (within 5 percentage points) or lower in the AMG 386 group relative to placebo.

Overall, no clinically significant trends in serum chemistry or hematology laboratory values were observed during the treatment period.

Conclusions: In regard to this study's primary endpoint, in the ITT population, the estimated hazard ratio for a PFS event in the AMG 386 versus placebo groups was 1.231 (80% CI 0.939 to 1.612), consistent with a 6% decrease in the risk of a PFS event to a 61% increase in the risk of a PFS event with AMG 386 treatment relative to placebo. Review of the data did not uncover the existence of any factors which may confound the observed PFS findings.

Regarding secondary survival and response endpoints, notable findings were observed with OS and ORR. At the time of the primary analysis, OS was trending opposite of PFS, with a hazard ratio for death of 0.901 (80% CI 0.635 to 1.279) if treated with AMG 386 versus placebo. However, at the time of the primary analysis approximately 60% of patients in both treatment

groups were censored. Additionally, historic response rates to FOLFIRI after failure of an oxaliplatin plus fluoropyrimidine based chemotherapy regimen are less than 5% (Tournigand et al, 2004; Sobrero et al, 2008); thus the ORR of 14.3% observed with AMG 386 treatment in this study is notable.

AMG 386 steady state median peak and trough concentrations were measured to be 221 and 15.6 µg/mL when co-administered with FOLFIRI, which was similar to those following monotherapy (Study 20040169). When comparing only C_{max} and C_{ss}, irinotecan exposure was comparable with or without AMG 386 administration, but the SN-38 and 5-FU exposure trended lower with AMG 386 co-administration than with placebo co-administration. However, variability was such that these trends could reasonably be seen by chance and no conclusion regarding drug-drug interactions can be made from these data. Intensive pharmacokinetic subset data were also inconclusive for an interaction of AMG386 with SN-38 or 5-FU. The gender difference in 5-FU exposure (higher in females than in males) is consistent with previous reports in the literature (Kubota, 2003; Yamashita et al, 2002; Milano et al, 1992).

Aside from the known toxicities associated with the FOLFIRI regimen, no unexpected toxicities were apparent in this study with the addition of AMG 386 to the regimen. The overall subject incidence of adverse events and serious adverse events was similar in the AMG 386 and placebo groups.

2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Trebananib (AMG 386)

Name of Active Ingredient: Trebananib (AMG 386)

Title of Study: A Phase 2, Randomized, Double-Blind, Placebo Controlled Study of AMG 386 in Combination with FOLFIRI in Subjects with Previously Treated Metastatic Colorectal Carcinoma

Investigators and Study Centers: This study was conducted at 38 sites in the United States, Europe, Russia, India, and Australia. Names and addresses of principal investigators are listed in Appendix 2.

Publications: None as of the date of this report

Study Period: 05 December 2008 (date first subject enrolled) to 01 May 2012 (early study closure date)

Development Phase: 2

Introduction and Objectives: This study was designed to evaluate the activity of trebananib (AMG 386), an antiangiogenic investigational product, as a second-line treatment in subjects with metastatic colorectal cancer. This abbreviated report summarizes data from the final analysis.

The primary analysis of this study was conducted using data as of 09 July 2010, at which time 27 subjects remained on treatment, and was reported in a full clinical study report (CSR) dated 29 March 2012. This report included analyses of safety, efficacy, pharmacokinetics, patient-reported outcomes (PRO), clinical immunology, and biomarker assessments. The present abbreviated report summarizes the final analysis of safety and efficacy, inclusive of the entire study period for all subjects and additional pharmacokinetic (PK) data for subjects who remained on treatment after the primary analysis. Updates to the primary analysis results, including efficacy and safety, are reported in this CSR; in some cases, it is specified where results were consistent with those presented in the primary analysis report.

The primary objective of the study was to estimate the treatment effect as measured by progression-free survival (PFS) of subjects receiving trebananib and 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) in combination compared with FOLFIRI and placebo. The secondary objectives were to evaluate other measures of treatment effect (objective response rate [ORR], duration of response [DOR], overall survival [OS]); to estimate PFS and other measures of efficacy by Kirsten rat sarcoma-2 virus *(KRAS)* status, to evaluate the relative dose intensity of trebananib and all FOLFIRI components; to evaluate the pharmacokinetics of trebananib (all subjects) and FOLFIRI components (subgroup of subjects at selected sites outside of Europe), to estimate the immunogenicity as assessed by the incidence of anti-trebananib antibody formation; to estimate the impact of trebananib on cancer-related symptoms based on PRO using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30); and to evaluate the safety and tolerability of the combination regimen of trebananib with FOLFIRI. Exploratory objectives are described in the study protocol (Appendix 1).

Methodology: Subjects were randomized 2:1 to the following treatment arms:

- Arm A: trebananib 10 mg/kg intravenously (IV) once weekly (QW), FOLFIRI once every 2 weeks (Q2W) (referred to as trebananib treatment group)
- Arm B: trebananib placebo IV QW, FOLFIRI Q2W (referred to as placebo treatment group)

Radiological imaging was performed every 8 weeks ± 1 week until disease progression, initiation of a new treatment or full withdrawal of consent. Subjects received study treatment until radiographic disease progression per Response Evaluation Criteria in Solid Tumor (RECIST v 1.0) with modifications (Appendix 1), clinical progression, unacceptable toxicity, subject withdrawal of consent, or death. Subjects were to return for a safety follow-up visit between 30 and 37 days from discontinuation of study treatment, and were to be followed for survival for up to 30 months from the date the last subject was randomized.

Due to a lack of scientific rationale to keep the study open until November 2012 as originally planned, this study was closed in May 2012. The number of subjects in the long term follow-up phase (planned to continue for 30 months after the last subject was randomized) was small (12%) and further data from these subjects were considered to have little impact on the final OS analysis, the safety analysis, or the conclusions drawn from the study.

Number of Subjects Planned: Approximately 138 subjects

Number of Subjects Enrolled: 144

Sex: 60 (42%) women and 84 (58%) men

Age: mean (standard deviation [SD]) was 55.2 (12.6) years (range 23 to 79)

Ethnicity (Race): 110 (76%) white or Caucasian, 2 (1%) black or African American, and 32 (22%) Asian

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men or women ≥ 18 years of age with histologically confirmed adenocarcinoma of the colon or rectum with metastatic disease which had progressed during, or within 6 months after the last dose of, 1 prior chemotherapy regimen for metastatic disease (a combination of a fluoropyrimidine-based chemotherapy and an oxaliplatin-based chemotherapy). Subjects had at least 1 uni-dimensionally measurable lesion per RECIST v 1.0 with modifications.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: Trebananib 10 mg/kg or placebo were administered IV QW. The manufacturing batch numbers of trebananib administered in this study were [redacted]. The manufacturing batch numbers of placebo administered in this study were [redacted]

Duration of Treatment: Subjects received study treatment until radiographic disease progression, clinical progression, unacceptable toxicity, withdrawal of consent or death.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: All subjects received FOLFIRI regimen (Q2W) which consisted of irinotecan 180 mg/m^2 IV, leucovorin 400 mg/m^2 IV, and 5-FU 400 mg/m^2 IV bolus, followed by 2400 mg/m^2 continuous IV infusion. Chemotherapy agents were obtained from commercial sources.

Study Endpoints

The primary endpoint was PFS, defined as the time from randomization date to date of disease progression (per RECIST v 1.0 with modifications) or death. Secondary efficacy endpoints included ORR; DOR; OS; PFS by *KRAS* status; change in tumor burden; time to response (TTR); time to progression (TTP); incidence of adverse events and significant laboratory changes from baseline; overall exposure, dose adjustments and rates of discontinuation for FOLFIRI; PK parameters (maximum observed serum concentration [C_{max}] and area under the serum concentration-time curve [AUC] of trebananib); PK parameters of FOLFIRI (5-FU: concentration at steady state [C_{ss}] and AUC; irinotecan and its active metabolite SN-38: C_{max} and AUC) in a subgroup of subjects in selected sites outside of Europe; incidence of anti-trebananib antibody formation; and change in PRO as assessed with the EORTC QLQ-C30. Exploratory endpoints are described in the study protocol (Appendix 1).

Statistical Methods: Analyses of PFS, OS, ORR, DOR, and TTR were conducted in the All Randomized Analysis Set. PFS and OS hazard ratios and 2-sided 80% confidence intervals (CIs) were calculated using Cox regression models stratified by the randomization factor (Eastern Cooperative Oncology Group [ECOG] status of 0 or 1). Kaplan-Meier (K-M) curves and K-M medians, if estimable, were provided. Safety assessments, including analyses of treatment-emergent adverse events; changes in laboratory values, electrocardiogram (ECG) parameters, and vital signs; and the incidence of anti-trebananib antibody formation, were provided for all randomized subjects who received at least 1 dose of study drug.

Summary of Results:

Subject Disposition: A total of 187 subjects were screened; 144 subjects were randomized to receive trebananib 10 mg/kg IV QW plus FOLFIRI Q2W (Arm A) or placebo IV QW plus FOLFIRI Q2W (Arm B). Ninety-four (99%) subjects randomized to the trebananib treatment group and 49 (100%) subjects randomized to the placebo treatment group received at least 1 dose of the study drug.

All subjects discontinued treatment. Disease progression was the most common reason for discontinuation of investigational product (75% and 76% in the trebananib and placebo groups, respectively) as well as for FOLFIRI (75% and 69%, respectively). More subjects in the trebananib treatment group discontinued investigational product due to an adverse event (12% compared with 4% in the placebo treatment group). The proportion of subjects discontinuing FOLFIRI due to an adverse event was comparable between the treatment groups (9% and 10%, respectively).

The most common reasons for study discontinuation were death and administrative decision (sponsor's decision to close the study).

Efficacy Results: Median PFS (80% CI) was 3.5 (3.2, 5.2) and 5.3 (4.0, 5.5) months for the trebananib and placebo treatment groups, respectively. The analysis of PFS, specified as a stratified Cox model (stratification factors: ECOG performance status of 0 or 1) to compare trebananib versus placebo, provided a hazard ratio (80% CI) of 1.248 (0.984, 1.584), (p-value = 0.23). For subjects within the mutant *KRAS* subgroup, median PFS was 2.9 and 5.5 months in the trebananib and placebo treatment groups, respectively, and the hazard ratio (80% CI) estimate for trebananib versus placebo was 2.186 (1.323, 3.614) (p-value = 0.046). For subjects within the wild-type *KRAS* subgroup, median PFS was 5.2 months in both trebananib and placebo treatments and the hazard ratio (80% CI) estimate for trebananib versus placebo was 1.138 (0.819, 1.580) (p-value = 0.61).

Median OS (80% CI) was 12.1 months and 11.4 months for subjects in the trebananib and placebo treatment groups, respectively. A stratified Cox regression analysis of OS provided a hazard ratio (80% CI) of 0.894 (0.692, 1.156), (p-value = 0.58) for trebananib relative to placebo.

For subjects within the mutant *KRAS* subgroup, median OS was 8.0 and 15.2 months in the trebananib and placebo treatment groups, respectively, and the hazard ratio (80% CI) estimate for trebananib versus placebo was 1.577 (0.945, 2.632) (p-value = 0.25). For subjects within the wild-type *KRAS* subgroup, median OS was 14.3 and 12.1 months in the trebananib and placebo treatment groups, respectively, and the hazard ratio (80% CI) estimate for trebananib versus placebo was 0.737 (0.520, 1.045) (p-value = 0.26).

The results of the ORR, DOR, TTP, and TTR analyses were consistent with the primary analysis.

Pharmacokinetics Results: Limited additional 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.

Antibody Results: No developing antibodies were detected during the final analysis. Pre-existing, non-neutralizing, binding antibodies were detected in 2 of 92 subjects who were treated with trebananib.

Safety Results: The overall subject incidence of adverse events was similar between the trebananib and placebo groups (97% and 98% in the trebananib and placebo groups, respectively). Grade 3 and higher adverse events occurred in 65% and 67% of subjects in the respective treatment groups. There were no treatment related trends in the overall severity of adverse events in the trebananib group compared with placebo (grade 3: 47%, 39% in trebananib and placebo groups, respectively; grade 4: 13%, 22%, and grade 5: 5%, 6%). Adverse events were reported as related to treatment with trebananib (or placebo) for 37% and 41% of subjects in the respective treatment groups, and to FOLFIRI treatment for 88% and 90% of subjects, respectively. Adverse events led to permanent discontinuation from the treatment phase (investigational product and FOLFIRI treatment) or study for 13% and 12% of subjects in the trebananib and placebo groups, respectively.

In general, the incidence of adverse events by Medical Dictionary for Regulatory Activities (MedDRA) preferred term was similar between the trebananib and placebo treatment groups. The most common adverse events occurring in ≥ 10% subjects in either treatment group were diarrhea (trebananib: 47%, placebo: 41%), nausea (44%, 39%), neutropenia (41%, 59%), asthenia (31%, 33%), decreased appetite (28%, 16%), alopecia (27%, 39%), fatigue (26%, 18%), peripheral edema (21%, 4%), constipation (20%, 18%), vomiting (17%, 39%), abdominal pain (15%, 14%), pyrexia (15%, 10%), leucopenia (13%, 14%), stomatitis (13%, 8%), cough (9%, 18%), anemia (6%, 24%), and mucosal inflammation (6%, 10%).

Serious adverse events were reported for 30% and 35% of subjects in the trebananib and placebo groups, respectively. The most frequently reported serious adverse events (ie, occurring in ≥ 5% subjects either treatment group) by preferred term (trebananib and placebo) were febrile neutropenia (2%, 6%), neutropenia (1%, 6%), abdominal pain (0%, 6%), and vomiting (0%, 6%). Treatment-related serious adverse events were reported for 18% and 24% of subjects in the trebananib and placebo treatment groups, respectively.

Edema, pleural effusion, and ascites are identified risks with trebananib administration. Edema adverse events were reported for 27% and 8% of subjects in the trebananib and placebo treatment groups, respectively, with 1 event of grade 3 or higher (lymphoedema, trebananib treatment group). The most common edema adverse event was peripheral edema (trebananib: 21%, placebo: 4%). No subjects had adverse events of pleural effusion. Adverse events of ascites were reported for 6 (6%) and 3 (6%) subjects in the trebananib and placebo treatment groups, respectively. The subject incidence of other potential risks (gastrointestinal perforation, hemorrhage, proteinuria, pulmonary embolism, and infusion reactions) and adverse events of interest (arterial and venous thromboembolic events, cardiac failure, hematologic toxicity, hypertension, hypothyroidism, impaired wound healing, pancreatic toxicity, and hypokalemia) was similar (within 5 percentage points) or lower in the trebananib group relative to placebo.

Overall, no clinically significant trends in serum chemistry or hematology laboratory values were observed during the treatment period.

Conclusions:

The results of the final analysis were consistent with those of the primary analysis.

In regard to the study's primary endpoint, in the randomized population, the estimated hazard ratio for a PFS event in the trebananib versus placebo groups was 1.248 (80% CI: 0.984 to 1.584). Review of the data did not uncover the existence of any factors which may confound the observed PFS findings.

Regarding the secondary endpoint of OS, the estimated hazard ratio for death was 0.894 (80% CI: 0.692 to 1.156) if treated with trebananib versus placebo, with 23% and 20% of subjects censored in the trebananib and placebo groups, respectively.

Aside from the known toxicities associated with the FOLFIRI regimen, no unexpected toxicities were apparent in this study with the addition of trebananib to the regimen. Aside from the identified risk of edema associated with trebananib, the overall subject incidence of adverse events and serious adverse events was similar in the trebananib and placebo groups.