2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA

Name of Finished Products: Ganitumab and conatumumab

Name of Active Ingredients: AMG 479 and AMG 655

Title of Study: A Phase 2, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of FOLFIRI in Combination With AMG 479 or AMG 655 Versus FOLFIRI for the Second-line Treatment of *KRAS*-mutant Metastatic Colorectal Carcinoma

Investigators and Study Centers: This study was conducted at a total of 49 centers in 10 countries (France, Hong Kong, Hungary, India, Italy, Poland, Russian Federation, Singapore, Spain, and United States). Study centers and investigators are listed in Appendix 4.

Publications: None

Study Period: This clinical study report includes results from the date of the first subject enrolled (31 March 2009) to the primary analysis data cutoff date (31 January 2011). Results after the primary analysis data cutoff date will be reported separately.

Development Phase: 2

Introduction and Objectives: Ganitumab, a fully human monoclonal IgG1 antibody against human insulin-like growth factor receptor type 1 (IGF-1R), is being developed as an anticancer drug to provide inhibitory effects on tumor growth and invasion in combination with standard cancer therapy, molecularly targeted therapy, or both. Ganitumab exerts its antitumor activity by blocking ligand binding (insulin-like growth factor-1 [IGF-1] and insulin-like growth factor-2 [IGF-2]) and inducing receptor internalization and degradation without cross-reacting with the insulin receptor. Evidence from nonclinical xenograft models of colorectal cancer shows that ganitumab is active as monotherapy and in combination with chemotherapy and other targeted agents commonly used in colon cancer treatment (eg, irinotecan, 5-fluorouracil [5-FU], and panitumumab).

Conatumumab, a fully human agonist monoclonal antibody (immunoglobulin type G1) targeting human death-receptor 5 (DR5), is being developed as an anticancer drug. Conatumumab mimics endogenous tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), binds DR5, and induces apoptosis in sensitive cells. Conatumumab demonstrates dose-dependent activity against colorectal cancer xenografts in vivo. The in vivo activity of conatumumab also is significantly enhanced when used in combination with 5-FU and irinotecan.

The primary objective was to estimate the treatment effect on progression-free survival (PFS) of conatumumab plus irinotecan/leucovorin/5-fluorouracil (5-FU) (FOLFIRI) or ganitumab plus FOLFIRI relative to FOLFIRI alone when administered as a second-line treatment for subjects with metastatic colorectal cancer (mCRC) whose tumors express mutant Kirsten rat sarcoma virus oncogene homolog (*KRAS*).

The secondary objectives were:

- To estimate treatment effect on overall survival, objective response rate (complete response + partial response), rates of disease control (ie, complete response + partial response + stable disease), duration of response, and time to response
- To evaluate the incidence of adverse events and significant laboratory abnormalities and the incidence of anti-conatumumab or anti-ganitumab antibody formation
- To evaluate treatment effect on patient-reported outcomes (PROs) using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire-core questionnaire (QLQ-C30) and the Functional Assessment of Cancer Therapy (FACT)/National Cancer Comprehensive Network (NCCN)-Colorectal Symptom Index (FCSI)
- To evaluate pharmacokinetics of conatumumab, ganitumab, and FOLFIRI components (irinotecan and 5-FU), and estimate the impact of administration of conatumumab and ganitumab on the pharmacokinetics of FOLFIRI components (irinotecan and 5-FU)

- To correlate treatment outcomes with tumor tissue analysis of somatic gene mutations that regulate the IGF-1R and death receptor (DR) pathways and other genes that are known to be involved in tumorigenesis

Methodology: This is an ongoing, phase 2, multicenter, randomized, double-blind, double-dummy, placebo-controlled study evaluating the safety and efficacy of FOLFIRI in combination with ganitumab or conatumumab relative to FOLFIRI alone for the second-line treatment of mutant *KRAS* mCRC. Eligible subjects were randomized in a 1:1:1 ratio to second-line therapy consisting of either:

- Arm A: Ganitumab-placebo plus conatumumab 10 mg/kg in combination with FOLFIRI every 14 days
- Arm B: Ganitumab 12 mg/kg plus conatumumab-placebo in combination with FOLFIRI every 14 days
- Arm C: Ganitumab-placebo plus conatumumab-placebo in combination with FOLFIRI every 14 days

Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1) and previous exposure to anti-vascular endothelial growth factor (VEGF) therapy in first-line treatment (yes versus no).

Cycles of chemotherapy plus investigational products (ganitumab, conatumumab, ganitumab-placebo, and conatumumab-placebo) were to be administered every 14 days (± 3 days) (not including the time to recover from toxicities). Subjects were permitted to receive protocol-specified therapy until disease progression (by modified Response Evaluation Criteria in Solid Tumors [RECIST version 1.0] guidelines or clinical progression), unacceptable toxicities, withdrawal of consent, death, or until 36 months after the last subject had been randomized. In the event the administration of any component of the FOLFIRI chemotherapy was discontinued for any reason other than disease progression, the other components of the FOLFIRI chemotherapy were to continue along with the investigational products. Subjects who became intolerant to all components of FOLFIRI chemotherapy were to continue investigational products until disease progression (radiographic per RECIST or clinical progression), unacceptable toxicities, withdrawal of consent, death, or until 36 months after the last subject has been randomized. Subjects who became intolerant to investigational products were to continue to receive FOLFIRI at the discretion of the investigator until disease progression (radiographic per RECIST or clinical progression), unacceptable toxicities, withdrawal of consent, death, or until 36 months after the last subject had been randomized. Subjects who remained on protocol-specified therapy 36 months after the last subject was randomized could be eligible for continued treatment with open-label ganitumab or conatumumab by protocol extension or as provided for by the local country's regulatory mechanism.

Subjects who discontinued protocol-specified therapy for disease progression or other reasons (except death) were followed for safety for 30 (+3) days, and for antibodies and pharmacokinetic assessment of ganitumab and conatumumab for 30 (+3) days and 60 (+14) days after the last study administration of protocol-specified therapy.

Subjects were followed for survival every 3 months (±14 days) starting from the date of the last administration of protocol-specified therapy until death or 36 months after last subject had been randomized, whichever was earlier. Any subject who discontinued protocol-specified therapy before radiographic disease progression or death continued to have radiological imaging performed at week 6, week 12, and every 8 weeks (± 7 days) thereafter during the long-term follow-up period. This procedure was used to assess disease status until disease progression (radiographic per RECIST or clinical progression), start of a new treatment, death, withdrawal of consent, administrative decision, or the end of the study, whichever was earlier.

An internal Amgen data review team (DRT) was established to review safety and pharmacokinetic data. Safety interim reviews were planned to occur after the first 18 and 36 subjects were randomized, had received at least 1 dose of investigational products (ganitumab, conatumumab, ganitumab-placebo, or conatumumab-placebo) in combination with FOLFIRI, and had the opportunity to complete 2 treatment cycles. Based on the length of time

between the second DRT review and the planned primary analysis for the study, the DRT conducted an additional safety review after the 100th subject received treatment.

Number of Subjects Planned: Approximately 150 subjects

Number of Subjects Enrolled: 155 subjects

Diagnosis and Main Criteria for Eligibility: The main inclusion criteria for subjects in this study included men or women ≥ 18 years of age with histologically confirmed adenocarcinoma of the colon or rectum with metastatic disease; mutant *KRAS* tumor status confirmed by central laboratory assessment; 1 prior anticancer therapy regimen for metastatic disease consisting of the combination of a fluoropyrimidine and oxaliplatin-based chemotherapy with or without anti-VEGF therapy and documented disease progression ≤ 6 months after the last dose of this prior anticancer therapy; measurable or nonmeasurable disease according to modified RECIST; ECOG performance status of 0 or 1; and adequate hematologic, renal, and hepatic function. A complete list of inclusion/exclusion criteria is provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Ganitumab, ganitumab-placebo, conatumumab, and conatumumab-placebo were considered investigational products in this study. Ganitumab and conatumumab were provided as a sterile, clear, colorless protein solution. Each glass vial contained 3.0 mL of investigational product with a concentration of 30 mg/mL (90 mg/vial). The listings of lot numbers by subject for all investigational products are provided in Appendix 18.

The dose of ganitumab was 12 mg/kg once every 2 weeks (Q2W) and the dose of conatumumab was 10 mg/kg Q2W. Investigational products were administered sequentially by intravenous (IV) infusion on day 1 of each cycle just before the administration of FOLFIRI chemotherapy.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: The FOLFIRI chemotherapy regimen (irinotecan with infusional 5-FU and leucovorin) was administered on day 1 of each treatment cycle after the administration of investigational products. Irinotecan (180 mg/m^2) was administered over approximately 90 minutes on day 1 of each cycle. Leucovorin (400 mg/m^2) was administered over approximately 2 hours during the irinotecan infusion but without mixing (lines could be connected at the IV port closest to the subject), immediately followed by a 5-FU bolus (2,400 mg/m^2) administered over approximately 2 to 4 minutes and a 5-FU continuous IV infusion administered via ambulatory pump over approximately 46 to 48 hours. Lot numbers were not collected.

Duration of Treatment: The expected median length of treatment was approximately 4 months. Subjects were treated with second-line treatment on study until one of the following occurred: disease progression (by modified RECIST criteria or clinical progression), unacceptable toxicities, withdrawal of consent, death, or until 36 months after the last subject had been randomized. Subjects were followed up for survival for up to 36 months from the date that the last subject had been randomized. The expected maximum duration of the study was approximately 56 months (ie, from the first subject randomized until approximately 36 months from the last subject randomized).

Study Endpoints:

Primary Endpoint

- Progression-free survival (defined as the number of days from the date of randomization to the first observation of disease progression [per modified RECIST or clinical progression, whichever occurred first], or death due to any cause, or date of censoring)

Secondary Endpoints

Efficacy

- Overall survival (defined as the number of days from the date of randomization to death from any cause, or if applicable, date of censoring)
- Objective response rate (defined as proportion of subjects with either a confirmed complete response or a confirmed partial response as determined by modified RECIST criteria and as evaluated by the investigator)

- Rate of disease control (defined as the number of subjects with a best overall response of stable disease or better [based on modified RECIST] divided by the number of subjects in the full analysis set with baseline measurable disease)
- Duration of response (defined as the number of days between the date of the first tumor response assessment with an outcome indicating an objective response through to the subsequent date of progression [based on modified RECIST, or clinical progression, whichever occurred first] or death due to any cause, or where applicable, date of censoring)
- Time to response (defined as time from the date of randomization to the first observation of an objective response in the subset of subjects who responded)

Pharmacokinetic

- Pharmacokinetic parameters (observed maximum concentration [C_{max}] and observed minimum concentration [C_{min}]) for conatumumab and ganitumab
- Pharmacokinetic parameters (C_{max}, C_{min}, and area under the curve [AUC]) for irinotecan and SN-38
- Pharmacokinetic parameters (concentrations over an approximately 48-hour infusion period) for 5-FU

Patient-reported Outcome (PROs)

- Changes (improvement or worsening) in PROs as assessed using the EORTC QLQ-C30 and the FCSI

Safety

- Incidence of adverse events and significant laboratory abnormalities
- Incidence of anti-conatumumab or anti-ganitumab antibody formation

Biomarker

- Tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R and/or apoptosis pathways and other genes that are known to be involved in the development and progression of solid tumors and correlation with treatment outcomes

Statistical Methods: The primary efficacy analysis was event-driven and was to occur when 100 subjects had experienced a PFS event (radiological disease progression or clinical progression, whichever occurred first) or death. The statistical analyses were descriptive and noninferential. The efficacy analysis was conducted on the full analysis set. For PFS and overall survival, the proportionality between treatment arms was assessed via examination of Kaplan-Meier survival and log(-log) survival curves. The primary method of analysis used a stratified Cox's proportional hazards model, and the estimated hazard ratio was presented with associated 80% and 95% confidence intervals (CIs) for ganitumab relative to placebo and conatumumab relative to placebo. Objective response rate and disease control rate were summarized descriptively with corresponding 95% CIs using the method described by Clopper and Pearson (1934). Duration of response was summarized for subjects with an objective response using Kaplan-Meier time-to-event curves with 95% CI estimates. Time to response was summarized using summary statistics.

Serum ganitumab and conatumumab, and plasma 5-FU, irinotecan, and SN-38 (the active metabolite of irinotecan) concentrations were summarized with descriptive statistics. [redacted] The effect of FOLFIRI on ganitumab or conatumumab pharmacokinetics was investigated by comparing the concentration exposures in the current study to those in the respective first-in-human study for each investigational product.

For PROs, the scores generated from the EORTC QLQ-C30 and FCSI were summarized descriptively for the following scales, as well as change from baseline, at each scheduled assessment by treatment arm: the 5 functional scales, 3 multi-item symptom scales,

6 single-item symptoms scales, the health-related quality of life (HRQOL) scale of the EORTC QLQ-C30, and the FCSI score.

Safety endpoints were analyzed using the safety analysis set, which included all randomized subjects who received at least 1 dose of ganitumab, conatumumab, or placebo; subjects in this analysis set were analyzed according to the treatment received. Adverse events were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. The subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events was summarized. Adverse events of interest were summarized separately for ganitumab (drug-related hepatotoxicity, hyperglycemia, infusion reaction, neutropenia, rash, thrombocytopenia, venous thromboembolic events, and sensorineural hearing loss) and for conatumumab (hypomagnesemia, hyponatremia, infusion reactions, and venous thromboembolic events). Clinical laboratory parameters and vital signs were summarized using descriptive statistics or shift tables. The incidence of subjects developing anti-ganitumab and anti-conatumumab antibodies was determined.

Summary of Results:

Subject Disposition: A total of 155 subjects were randomized into the study. Of these subjects, 52 were randomized to receive ganitumab, 51 subjects were randomized to receive conatumumab, and 52 were randomized to receive placebo. As of the primary analysis cutoff date, 75%, 71%, and 73% of the subjects in the ganitumab, conatumumab, and placebo treatment groups, respectively, discontinued investigational product. The 2 most common reasons for withdrawal from investigational product were disease progression (ganitumab: 58%, conatumumab: 49%, placebo: 63%) and adverse event (10%, 12%, 2%).

Forty-two percent, 37%, and 42% of the subjects in the ganitumab, conatumumab, and placebo treatment groups, respectively, discontinued the study. The 2 most common reasons for study withdrawal were death (ganitumab: 31%, conatumumab: 33%, placebo: 35%) and full consent withdrawn (8%, 4%, 4%).

Baseline Demographics:

Sex: 74 men (48%); 81 women (52%)

Age: mean (standard deviation [SD]) 57.5 (10.5) years (range: 28 to 81)

Ethnicity/Race: 119 (77%) white; 9 (6%) black; 25 (16%) Asian; 2 (1%) Hispanic or Latino

Efficacy Results: All efficacy evaluations are presented separately for ganitumab and conatumumab.

Ganitumab: The primary analysis of PFS, specified as a stratified Cox model (stratification factors: ECOG performance status and prior anti-VEGF exposure) comparing ganitumab with placebo, provided a hazard ratio estimate (95% CI) of 1.01 (0.61, 1.66) ($p = 0.998$, stratified log-rank test). The median PFS time was 4.5 months in the ganitumab treatment group and 4.6 months in the placebo treatment group. Results of the secondary efficacy and sensitivity analyses were consistent with the primary analysis.

The overall survival data are immature, with 69% of the subjects in the ganitumab treatment group and 65% of the subjects in the placebo treatment group censored at the time of the primary analysis. The overall survival unstratified hazard ratio was 0.92 (95% CI: 0.46, 1.84). The median overall survival was 12.2 months in the ganitumab treatment group and 9.6 months in the placebo treatment group.

The confirmed objective response rate was 8% (4 subjects) in the ganitumab treatment group and 2% (1 subject) in the placebo treatment group (all partial responses). The disease control rate was similar between the ganitumab and placebo treatment groups at week 6 (67% versus 65%), week 12 (45% versus 47%), and week 18 (27% versus 27%). Of the 4 subjects in the ganitumab treatment group who had a confirmed response, the median duration of response was 5.6 months and the median time to response was 4.6 months. The duration of response and the time to response was 5.2 months and 1.4 months, respectively, for the 1 subject in the placebo treatment group who had a confirmed response.

A higher proportion of subjects in ganitumab treatment group (6 of 52 subjects) had a decrease in the sum of the longest diameters (SLD) of 30% to 50% compared with the placebo treatment group (1 of 52 subjects). A higher proportion of subjects in the placebo treatment group (16 of 52 subjects) had an increase in SLD of > 0% compared with the ganitumab treatment group (9 of 52 subjects). No other differences in subsets of decreases in SLD were observed between treatment groups.

Conatumumab: The primary analysis of PFS, specified as a stratified Cox model (stratification factors: ECOG performance status and prior anti-VEGF exposure) comparing conatumumab with placebo, provided a hazard ratio estimate (95% CI) of 0.69 (0.41, 1.14) (p = 0.147, stratified log-rank test). The median PFS time was 6.5 months in the conatumumab treatment group and 4.6 months in the placebo treatment group. Results of the secondary efficacy and sensitivity analyses were consistent with the primary analysis.

The overall survival data are immature, with 67% of the subjects in the conatumumab treatment group and 65% of the subjects in the placebo treatment group censored at the time of the primary analysis. The overall survival unstratified hazard ratio was 0.84 (95% CI: 0.43, 1.64) (p = 0.610). The median overall survival was 12.3 months in the conatumumab treatment group and 9.6 months in the placebo treatment group.

The confirmed objective response rate was 14% (7 subjects) in the conatumumab treatment group and 2% (1 subject) in the placebo treatment group (all partial responses). The disease control rate was similar between the conatumumab and placebo treatment groups at week 6 (69% versus 65%) and week 12 (53% versus 47%). At week 18, the disease control rate was higher in the conatumumab treatment group (37%) compared with the placebo treatment group (27%). Of the 7 subjects in the conatumumab treatment group who had a confirmed response, the median duration of response was 5.3 months and the median time to response was 2.6 months. The duration of response and the time to response was 5.2 months and 1.4 months, respectively, for the 1 subject in the placebo treatment group who had a confirmed response.

A higher proportion of subjects in conatumumab treatment group (5 of 51 subjects) had a decrease in SLD of 30% to 50% compared with the placebo treatment group (1 of 52 subjects). A higher proportion of subjects in the placebo treatment group (16 of 52 subjects) had an increase in SLD of > 0% compared with the conatumumab treatment group (12 of 51 subjects). No other differences in subsets of decreases in SLD were observed between treatment groups.

Pharmacokinetic Results: Pharmacokinetic assessments were performed for ganitumab, conatumumab, irinotecan, SN-38, and 5-FU.

Ganitumab: Following 12 mg/kg Q2W IV infusion, the mean (SD) preinfusion concentration (C_{min}) in the fifth cycle (steady state) was 33.5 (16.5) µg/mL. Additional analysis was performed to compare the exposures over cycles with historical data of ganitumab monotherapy under the same regimen in subjects with advanced solid tumors (Study 20050118). The exposure levels were found to be comparable with or without coadministration of FOLFIRI.

Conatumumab: Following 10 mg/kg Q2W IV infusion, the mean (SD) preinfusion concentration (C_{min}) in the fifth cycle (steady state) was 92.4 (29.4) µg/mL. Additional analysis was performed to compare the exposures over cycles with historical data of conatumumab monotherapy under the same regimen in subjects with advanced solid tumors (Study 20050171). The exposure levels were found to be comparable with or without coadministration of FOLFIRI.

Irinotecan and SN-38 (the active metabolite): Following IV infusion of 180 mg/m^2 irinotecan, mean (SD) irinotecan area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) values were 12000 (2420), 14300 (3020), and 12400 (1500) ng•hr/mL in the ganitumab, conatumumab, and placebo treatment groups, respectively. The mean SN-38 $AUC_{0\text{-}inf}$ (SD) values were 354 (35), 345 (116), and 364 (124) ng•hr/mL, respectively. Because comparable irinotecan and SN-38 exposures were observed in the different treatment groups, coadministration with ganitumab or conatumumab did not appear to affect the pharmacokinetics of irinotecan or its metabolite SN-38.

5-FU: Following the protocol-specified dosing regimen, highly variable individual 5-FU concentrations were observed during the 48-hour infusion period. Nevertheless, the concentration ranges in ganitumab, conatumumab, and placebo treatment groups were comparable, and the median 5-FU concentrations at 24 hours (C_{24hr}) were 490, 371, 450 ng/mL,

respectively, in cycle 1 and 453, 475, and 389 ng/mL, respectively, in cycle 3. These results indicate that coadministration with ganitumab or conatumumab did not appear to affect the pharmacokinetics of 5-FU.

Patient-reported Outcomes Results: The ganitumab, conatumumab, and placebo treatment groups were generally similar at baseline for each EORTC QLQ-C30 and FCSI parameter. Results for the EORTC QLQ-C30 and FCSI analyses did not demonstrate any treatment-related differences during the course of the study.

Safety Results: All safety evaluations are presented separately for ganitumab and conatumumab.

Ganitumab: The overall incidence of adverse events was similar for the ganitumab and placebo treatment groups (92% and 96%, respectively). The most common adverse events (≥ 20% of the subjects in either treatment group) were diarrhea (ganitumab: 43%, placebo: 41%), neutropenia (47%, 37%), nausea (35%, 33%), fatigue (29%, 22%), vomiting (27%, 27%), anemia (27%, 10%), thrombocytopenia (24%, 6%), stomatitis (20%, 20%), decreased appetite (20%, 16%), alopecia (18%, 22%), asthenia (16%, 24%), and constipation (14%, 33%).

The subject incidence of grade ≥ 3 treatment-emergent adverse events was higher in the ganitumab treatment group (55%) compared with the placebo treatment group (47%). The most common grade ≥ 3 adverse events (occurring in ≥ 2 subjects in either treatment group) were neutropenia (ganitumab: 25%, placebo: 18%), diarrhea (2%, 10%), intestinal obstruction (6%, 8%), abdominal pain (4% each), vomiting (2%, 6%), anemia (8%, 4%), fatigue (2%, 4%), asthenia (2%, 6%), hyperglycemia (8%, 4%), leukopenia (6%, 0%), and mucosal inflammation (0%, 4%). The difference between treatment groups in grade ≥ 3 adverse events is mainly driven by hematologic adverse events (ie, leukopenia and anemia), and adverse events reflecting the known potential or identified risks of ganitumab (ie, neutropenia and hyperglycemia). No new safety signals appear to be reflected in this difference.

The subject incidence of serious adverse events was higher in the ganitumab treatment group (31%) compared with the placebo treatment group (24%). The most common serious adverse events (≥ 2 subjects in either treatment group) were intestinal obstruction (ganitumab: 6%, placebo: 4%), abdominal pain (4%, 2%), diarrhea (2%, 6%), vomiting (2%, 4%), and mucosal inflammation (0%, 4%). The difference between treatment groups in the incidence rate of serious adverse events is mainly driven by gastrointestinal events of abdominal pain and intestinal obstruction. These serious events of intestinal obstruction were due to either disease progression or intra-abdominal adhesions and were not reported to be related to ganitumab.

Two subjects in the ganitumab treatment group experienced fatal treatment-emergent adverse events. The fatal adverse event for Subject [redacted] was rectal cancer (this subject's primary cause of death is listed as disease progression), and for Subject [redacted] was diabetic ketoacidosis; both events occurred within 30 days after the last dose of investigational product and were not reported to be related to investigational product.

Two subjects (4%) in the ganitumab treatment group and 1 subject (2%) in the placebo treatment group withdrew from the study due to an adverse event. A higher proportion of subjects in the ganitumab treatment group (14%) experienced adverse events that led to discontinuation of any protocol specified therapy compared with subjects in the placebo treatment group (8%).

Overall, median post-treatment values were generally within normal range and/or were similar to baseline for most of the clinical laboratory parameters.

Despite never having received a dose of ganitumab, 1 subject in the placebo treatment group and 1 subject in the conatumumab treatment group, who were negative at baseline, tested positive for anti-ganitumab antibodies during the treatment period. In addition, 1 subject in the ganitumab treatment group, who was negative at baseline, tested positive for anti-ganitumab binding antibodies during the treatment period. No neutralizing antibodies were detected in any of the subjects. Anti-ganitumab antibodies detected at baseline or during treatment with placebo or conatumumab are likely to represent cross-reactive antibodies that are present as a consequence of molecular mimicry.

Conatumumab: The overall incidence of adverse events was similar for the conatumumab and placebo treatment groups (96% and 96%, respectively). The most common adverse events (≥ 20% of the subjects in either treatment group) were diarrhea (conatumumab: 58%, placebo:

41%), neutropenia (54%, 37%), nausea (36%, 33%), fatigue (22%, 22%), vomiting (28%, 27%), anemia (20%, 10%), stomatitis (8%, 20%), decreased appetite (24%, 16%), alopecia (26%, 22%), asthenia (30%, 24%), abdominal pain (24%, 16%), and constipation (16%, 33%).

The subject incidence of grade ≥ 3 treatment-emergent adverse events was higher in the conatumumab treatment group (72%) compared with the placebo treatment group (47%). The most common grade ≥ 3 adverse events (occurring in ≥ 2 subjects in either treatment group) were neutropenia (conatumumab: 30%, placebo: 18%), diarrhea (18%, 10%), intestinal obstruction (4%, 8%), abdominal pain (8%, 4%), vomiting (8%, 6%), anemia (4% each), fatigue (8%, 4%), asthenia (6% each), hyperglycemia (0%, 4%), dehydration (6%, 2%), decreased appetite (8%, 0%), weight decreased (6%, 0%), increased aspartate aminotransferase (AST) (4%, 0%), mucosal inflammation (2%, 4%), abdominal distension (4%, 0%), hypertension (4%, 0%), nausea (4%, 0%), and pyrexia (4%, 0%). The higher incidence of neutropenia, diarrhea, abdominal pain, and fatigue in the conatumumab group accounts for most of the overall difference between treatment groups in grade ≥ 3 adverse events.

The subject incidence of serious adverse events was higher in the conatumumab treatment group (40%) compared with the placebo treatment group (24%). The most common serious adverse events (≥ 2 subjects in either treatment group) were diarrhea (conatumumab: 10%, placebo: 6%), intestinal obstruction (4%, 4%), vomiting (6%, 4%), pyrexia (8%, 0%), dehydration (6%, 0%), and chest pain (4%, 0%). The higher incidence of diarrhea, pyrexia, and dehydration in the conatumumab group accounts for most of the overall difference between treatment groups in serious adverse events.

Two subjects in the conatumumab treatment group experienced treatment-emergent fatal adverse events. The fatal adverse event for Subject [redacted] was colorectal cancer (this subject's primary cause of death is listed as disease progression), and the fatal adverse event for Subject [redacted] was "death" (primary cause of death was "other" with further information noted as unknown death upon arrival at the hospital).

One subject (2%) in the conatumumab treatment group and 1 subject (2%) in the placebo treatment group withdrew from the study due to an adverse event. A higher proportion of subjects in the conatumumab treatment group (16%) experienced adverse events that led to discontinuation of any protocol specified therapy compared with subjects in the placebo treatment group (8%).

Overall, median post-treatment values were generally within normal range and/or were similar to baseline for most of the clinical laboratory parameters. One subject (3%) in the conatumumab treatment group, who was negative at baseline, tested positive for anti-conatumumab binding and neutralizing antibodies during the treatment period.

Conclusions: This was a well-controlled study. Demographics and baseline disease characteristics were balanced across treatment groups and representative of a second-line mCRC population.

The addition of ganitumab to FOLFIRI as second-line treatment did not appear to improve PFS in subjects with mutant *KRAS* mCRC over FOLFIRI alone. The hazard ratio point estimate of 1.01 (95% CI: 0.61, 1.66) for ganitumab plus FOLFIRI compared with FOLFIRI alone suggests no effect of ganitumab on PFS; however, the data could be consistent with either substantial benefit (hazard ratio = 0.61) or harm (hazard ratio = 1.66). Because of the low proportion of death events, the overall survival data are immature. The confirmed objective response rate was higher in the ganitumab treatment group compared with the placebo treatment group and the time to response also was longer.

This study showed a higher incidence of certain serious adverse events in the ganitumab treatment group as compared with the placebo treatment group, which were mainly reflective of gastrointestinal system organ class events and disease progression. In addition, the grade ≥ 3 adverse events, which were numerically higher in the ganitumab treatment group vs the placebo treatment group, were consistent with the known safety profile observed to date with ganitumab, including events identified as events of interest (neutropenia and hyperglycemia). No new safety risks associated with ganitumab treatment were identified.

The addition of conatumumab to FOLFIRI as second-line treatment resulted in PFS that was numerically higher than treatment with FOLFIRI alone in subjects with mutant *KRAS* mCRC. The hazard ratio estimate was 0.69 (95% CI: 0.41, 1.14) in favor of conatumumab treatment group, suggesting that the addition of conatumumab to FOLFIRI may improve outcome in this patient population and additional studies may be warranted. Because of the low proportion of death events, the overall survival data are immature. The confirmed objective response rate was higher in the conatumumab treatment group compared with the placebo treatment group.

This study showed higher incidences of grade ≥ 3 adverse events of neutropenia, diarrhea, abdominal pain, and fatigue and higher incidences of serious adverse events of diarrhea, pyrexia, and dehydration in the conatumumab treatment group versus the placebo treatment group. A review of the safety data observed in this study compared with the safety data in the monotherapy setting and with chemotherapy backbone (FOLFIRI) suggests that these events most likely reflect the adverse events associated with the chemotherapy backbone.

FOLFIRI coadministration did not appear to affect the pharmacokinetics of ganitumab and conatumumab. Likewise, ganitumab or conatumumab coadministration did not appear to affect pharmacokinetics of irinotecan and 5-FU.

SYNOPSIS

Name of Sponsor: Amgen, Inc., Thousand Oaks, CA

Name of Finished Product: Ganitumab and conatumumab

Name of Active Ingredient: AMG 479 and AMG 655

Title of Study: A Phase 2, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of FOLFIRI in Combination With AMG 479 or AMG 655 Versus FOLFIRI for the Second-line Treatment of *KRAS*-mutant Metastatic Colorectal Carcinoma

Investigator(s) and Study Center(s): This study was conducted at 49 centers in 10 countries (France, Hong Kong, Hungary, India, Italy, Poland, Russian Federation, Singapore, Spain, and United States). Study centers and investigators are listed in Appendix 2.

Publication(s): Cohn AL, Tabernero J, Maurel J, et al. Conatumumab (CON) + FOLFIRI (F) or Ganitumab (GAN) + F for Second-line Treatment of Mutant (MT) *KRAS* Metastatic Colorectal Cancer (mCRC) [poster]. ASCO Gastrointestinal Cancers Symposium, 2012. Abstract 534.

Study Period: The first subject was enrolled 31 March 2009; the last subject's final visit was 04 June 2012.

Development Phase: 2

Objectives: The primary objective was to estimate the treatment effect on progression-free survival (PFS) of conatumumab plus FOLFIRI or ganitumab plus FOLFIRI relative to FOLFIRI alone when administered as a second-line treatment for subjects with metastatic colorectal cancer (mCRC) whose tumors express mutant-type Kirsten rat sarcoma virus oncogene homolog (*KRAS*).

The secondary objectives were:

- To estimate treatment effect on overall survival (OS), objective response rate (complete response + partial response), rates of disease control (ie, complete+ partial + stable disease), duration of response, and time to response.
- To evaluate the incidence of adverse events and significant laboratory abnormalities and the incidence of anti-conatumumab or anti-ganitumab antibody formation.
- To evaluate treatment effect on patient-reported outcomes (PROs) using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire - core questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy (FACT)/National Cancer Comprehensive Network (NCCN) - Colorectal Symptom Index (FCSI).
- To evaluate pharmacokinetics of conatumumab, ganitumab, and FOLFIRI components (irinotecan and 5-FU) and estimate the impact of administration of conatumumab and ganitumab on the pharmacokinetics of FOLFIRI components (irinotecan and 5-FU).
- To correlate treatment outcomes with tumor tissue analysis of somatic gene mutations that regulate the insulin-like growth factor receptor type 1 (IGF-1R) and death receptor pathways and other genes that are known to be involved in tumorigenesis.

Exploratory objectives are located in the clinical protocol (Appendix 1).

Methodology:

This was a phase 2, multicenter, randomized, double-blind, double-dummy, placebo-controlled study evaluating the safety and efficacy of FOLFIRI in combination with ganitumab or conatumumab relative to FOLFIRI alone for the second-line treatment of *KRAS*-mutant mCRC. Eligible subjects were randomized in a 1:1:1 ratio to second-line therapy consisting of one of the following:

- Arm A: Ganitumab-placebo plus conatumumab 10 mg/kg in combination with FOLFIRI every 14 days
- Arm B: Ganitumab 12 mg/kg plus conatumumab-placebo in combination with FOLFIRI every 14 days
- Arm C: Ganitumab-placebo plus conatumumab-placebo in combination with FOLFIRI every 14 days

Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and previous exposure to anti-vascular endothelial growth factor (VEGF) therapy in first line (yes vs no).

Cycles of chemotherapy plus investigational products (ganitumab, conatumumab, ganitumab-placebo, and conatumumab-placebo) were to be administered every 14 days (± 3 days) (not including the time to recover from toxicities). Subjects were permitted to receive protocol-specified therapy until disease progression (by modified Response Evaluation Criteria in Solid Tumors [RECIST] version 1.0] guidelines or clinical progression), unacceptable toxicities, withdrawal of consent, death, or 36 months after the last subject had been randomized. In the event the administration of any component of the FOLFIRI chemotherapy was discontinued for any reason other than disease progression, the other components of the FOLFIRI chemotherapy were to continue along with the investigational products. Subjects who became intolerant to all components of FOLFIRI chemotherapy were to continue investigational products until disease progression (radiographic per RECIST or clinical progression), unacceptable toxicities, withdrawal of consent, death, or 36 months after the last subject had been randomized. Subjects who became intolerant to investigational products were to continue to receive FOLFIRI at the discretion of the investigator until disease progression (radiographic per RECIST or clinical progression), unacceptable toxicities, withdrawal of consent, death, or 36 months after the last subject had been randomized. Subjects who remained on protocol-specified therapy 36 months after the last subject was randomized could be eligible for continued treatment with open-label ganitumab or conatumumab by extension protocol or as provided for by the local country's regulatory mechanism.

Subjects who discontinued protocol-specified therapy for disease progression or other reasons (except death) were followed for safety for 30 (+ 3) days and for antibodies and pharmacokinetic assessment of ganitumab and conatumumab for 30 (+ 3) days and 60 (+ 14) days after the last study administration of protocol-specified therapy.

Subjects were followed for survival every 3 months (±14 days) starting from the date of the last administration of protocol-specified therapy until death or 36 months after last subject was randomized, whichever was earlier. Any subject who discontinued protocol-specified therapy before radiographic disease progression or death continued to have radiological imaging performed at week 6, week 12, and every 8 weeks (± 7 days) thereafter during the long-term follow-up period. This procedure was used to assess disease status until disease progression (radiographic per RECIST or clinical progression), start of a new treatment, death, withdrawal of consent, administrative decision, or the end of the study, whichever was earlier.

An internal Amgen data review team (DRT) was established to review safety and pharmacokinetic data. Safety interim reviews were planned to occur after the first 18 and 36 subjects were randomized, had received at least 1 dose of investigational products (ganitumab, conatumumab, ganitumab-placebo, or conatumumab-placebo) in combination with FOLFIRI, and had the opportunity to complete 2 treatment cycles. Based on the length of time between the second DRT review and the planned primary analysis for the study, the DRT conducted an additional safety review after the 100th subject received treatment.

The primary analysis data, using a data cutoff date of 31 January 2011, were presented in the primary analysis clinical study report dated 15 October 2011. The current report summarizes final analysis data (all data). Table 1 provides a summary of the data summarized in each clinical study report.

Table 1. Data Summarized in the Primary and Final Analysis Clinical Study Reports Study 20060579

Data Type	Primary Analysis CSR (31 January 2011 Data Cutoff)	Final Analysis CSR
Subject disposition	X	X
Demographic and baseline characteristics	X	–
Efficacy - OS, PFS	X	X
Efficacy - overall response, duration of response, time to response	X	–
Safety - adverse events, adverse events of interest, laboratory evaluations	X	X
Safety - ECOG, vital signs, ECGs, concomitant medications	X	–
PRO	X	–
PK	X	X
Antibody	X	X
Biomarker	X	–

CSR = clinical study report; – = no data analysis performed; OS = overall survival; PFS = progression-free survival, ECOG = Eastern Cooperative Oncology Group, ECG = electrocardiogram, PRO = patient-reported outcome, PK = pharmacokinetics.

Number of Subjects Planned: Approximately 150 subjects

Number of Subjects Enrolled: 155 subjects

Diagnosis and Main Criteria for Eligibility: The main inclusion criteria for subjects in this study included men or women ≥ 18 years of age with histologically confirmed adenocarcinoma of the colon or rectum with metastatic disease; mutant *KRAS* tumor status confirmed by central laboratory assessment; 1 prior anticancer therapy regimen for metastatic disease consisting of the combination of a fluoropyrimidine and oxaliplatin-based chemotherapy with or without anti-VEGF therapy and documented disease progression ≤ 6 months after the last dose of this prior anticancer therapy; measurable or nonmeasurable disease according to modified RECIST; ECOG performance status of 0 or 1; and adequate hematologic, renal, and hepatic function. A complete list of inclusion/exclusion criteria is provided in section 7.5 of the primary analysis clinical study report.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Ganitumab, ganitumab-placebo, conatumumab, and conatumumab-placebo were considered investigational products in this study. The listings of lot numbers by subject for all investigational products are provided in Listing 14-1.1, final analysis (FA).

The dose of ganitumab was 12 mg/kg once every 2 weeks (Q2W) and the dose of conatumumab was 10 mg/kg Q2W. Investigational products were administered sequentially by intravenous (IV) infusion on day 1 of each cycle just before the administration of FOLFIRI chemotherapy.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: The FOLFIRI chemotherapy regimen (irinotecan with infusional 5-FU and leucovorin) was administered on day 1 of each treatment cycle after the administration of investigational products. Irinotecan (180 mg/m^2) was administered over approximately 90 minutes on day 1 of each cycle.

Leucovorin (400 mg/m^2) was administered over approximately 2 hours during the irinotecan infusion but without mixing (lines could be connected at the IV port closest to the subject), immediately followed by a 5-FU bolus (400 mg/m^2) administered over approximately 2 to 4 minutes and a 5-FU continuous IV infusion (2400 mg/m^2) administered via ambulatory pump over approximately 46 to 48 hours. Lot numbers were not collected.

Duration of Treatment: The expected median length of treatment was approximately 4 months. Subjects were treated with second-line treatment on study until one of the following occurred: disease progression (by modified RECIST criteria or clinical progression), unacceptable toxicities, withdrawal of consent, death, or 36 months after the last subject had been randomized. Subjects were followed for survival for up to 36 months from the date that the last subject had been randomized.

Study Endpoints:

The following is a full list of endpoints from the study (additional exploratory endpoints are provided in the protocol located in Appendix 1). Some endpoints, as indicated below, were presented in the primary analysis clinical study report and are not included in the present clinical study report.

Primary Endpoint

- Progression-free survival (defined as the number of days from the date of randomization to the first observation of disease progression [per modified RECIST or clinical progression, whichever occurred first], or death due to any cause, or date of censoring)

Secondary Endpoints

- Overall survival (defined as the number of days from the date of randomization to death from any cause, or if applicable, date of censoring)
- Objective response rate (defined as proportion of subjects with either a confirmed complete response or a confirmed partial response as determined by modified RECIST criteria and as evaluated by the investigator) (presented in the primary analysis clinical study report)
- Rate of disease control (defined as the number of subjects with a best overall response of stable disease or better [based on modified RECIST] divided by the number of subjects in the full analysis set with baseline measurable disease) (presented in the primary analysis clinical study report)
- Duration of response (defined as the number of days between the date of the first tumor response assessment with an outcome indicating an objective response through to the subsequent date of progression [based on modified RECIST or clinical progression, whichever occurred first], or death due to any cause, or where applicable, date of censoring) (presented in the primary analysis clinical study report)
- Time to response (defined as time from the date of randomization to the first observation of an objective response in the subset of subjects who responded) (presented in the primary analysis clinical study report)

Pharmacokinetic Endpoints

- Pharmacokinetic parameters (observed maximum concentration [C_{max}] and observed minimum concentration [C_{min}]) for conatumumab and ganitumab
- Pharmacokinetic parameters (C_{max}, C_{min}, and area under the curve [AUC]) for irinotecan and SN-38
- Pharmacokinetic parameters (concentrations over an approximately 48-hour infusion period) for 5-FU

Patient-reported Outcome

- Changes (improvement or worsening) in PROs as assessed using the EORTC QLQ-C30 and the FCSI (presented in the primary analysis clinical study report)

Safety

- Incidence of adverse events and significant laboratory abnormalities
- Incidence of anti-conatumumab or anti-ganitumab antibody formation

Biomarker

- Tumor tissue analysis of somatic gene mutations that function to regulate the IGF-1R and/or apoptosis pathways and other genes that are known to be involved in the development and progression of solid tumors and correlation with treatment outcomes (presented in the primary analysis clinical study report)

Statistical Methods: The methodologies for all of the efficacy and safety analyses have been described previously in the primary analysis clinical study report, dated 15 October 2011. The methodologies for the key efficacy and safety analyses presented in the present report are described below.

The primary efficacy analysis was event-driven and was to occur when 100 subjects had experienced a PFS event (radiological disease progression or clinical progression, whichever occurred first) or death. The statistical analyses were descriptive and noninferential. The efficacy analysis was conducted on the full analysis set. For PFS and OS, the proportionality between treatment arms was assessed via examination of Kaplan-Meier survival and log(-log) survival curves. The primary method of analysis used a stratified Cox's Proportional Hazards model, and the estimated hazard ratio was presented with associated 80% and 95% confidence intervals (CIs) for ganitumab relative to placebo and conatumumab relative to placebo.

Serum ganitumab and conatumumab and plasma 5-FU, irinotecan, and SN-38 (the active metabolite of irinotecan) concentrations were summarized with descriptive statistics. [redacted] The effect of FOLFIRI on ganitumab or conatumumab pharmacokinetics was investigated by comparing the concentration exposures in the current study to those in the respective first-in-human study for each investigational product.

Safety endpoints were analyzed using the safety analysis set, which included all randomized subjects who received at least 1 dose of ganitumab, conatumumab, or placebo; subjects in this analysis set were analyzed according to the treatment received. Adverse events were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0. Adverse events of interest were summarized separately for ganitumab (drug-related hepatotoxicity, hyperglycemia, infusion reaction, neutropenia, rash, thrombocytopenia, venous thromboembolic events, and sensorineural hearing loss) and for conatumumab (hypomagnesemia, hyponatremia, infusion reactions, and venous thromboembolic events). Clinical laboratory parameters were summarized using descriptive statistics or shift tables. The incidence of subjects developing anti-ganitumab and anti-conatumumab antibodies was determined.

Summary of Results:

Final results from key efficacy and safety analyses are presented in the present clinical study report, and comparisons have been made back to the primary analysis report where applicable.

Subject Disposition:

A total of 155 subjects were randomized to the study: 52 subjects to the ganitumab treatment arm, 51 to the conatumumab treatment arm, and 52 to the placebo treatment arm. At the time of the primary analysis, 30 subjects in the ganitumab treatment arm, 32 subjects in the conatumumab treatment arm, and 30 subjects in the placebo treatment arm were ongoing in the

study (Table 14-1.2, primary analysis [PA]). At the time of the final analysis, all subjects had discontinued the study (Table 14-1.1, FA). In the final analysis, the most common reason for discontinuing the study was death (39 [75%] subjects in the ganitumab arm, 40 [78%] subjects in the conatumumab arm, and 35 [67%] subjects in the placebo arm).

Of the subjects randomized to each of the treatments, 1 subject in the ganitumab arm never received investigational product, 1 subject in the conatumumab arm and 2 subjects in the ganitumab arm never received leucovorin and 5-FU, and 1 subject in the ganitumab arm never received irinotecan (Table 14-1.2, FA). With respect to all of the protocol-specified treatments, overall, the most common reason for discontinuation of the treatment was disease progression: for investigational product, the percentages in the ganitumab, conatumumab, and placebo arms were 79%, 71%, and 85%, respectively; for leucovorin and 5-FU, the percentages were 79%, 67%, and 85%; and for irinotecan, the percentages were 77%, 67%, and 85%.

As of the final analysis, the median number of months on study was 9.6 for ganitumab, 12.3 for conatumumab, and 9.6 for placebo (Table 14-1.3, FA).

Subject Demographics: From the primary analysis clinical study report:

Sex: 74 men (48%); 81 women (52%)

Age: mean (standard deviation [SD]) 57.5 (10.5) years (range: 28 to 81)

Ethnicity (Race): 119 (77%) white; 9 (6%) black; 25 (16%) Asian; 2 (1%) Hispanic or Latino

Efficacy Results:

Efficacy results below are presented separately for ganitumab and conatumab.

Ganitumab

Progression-free Survival

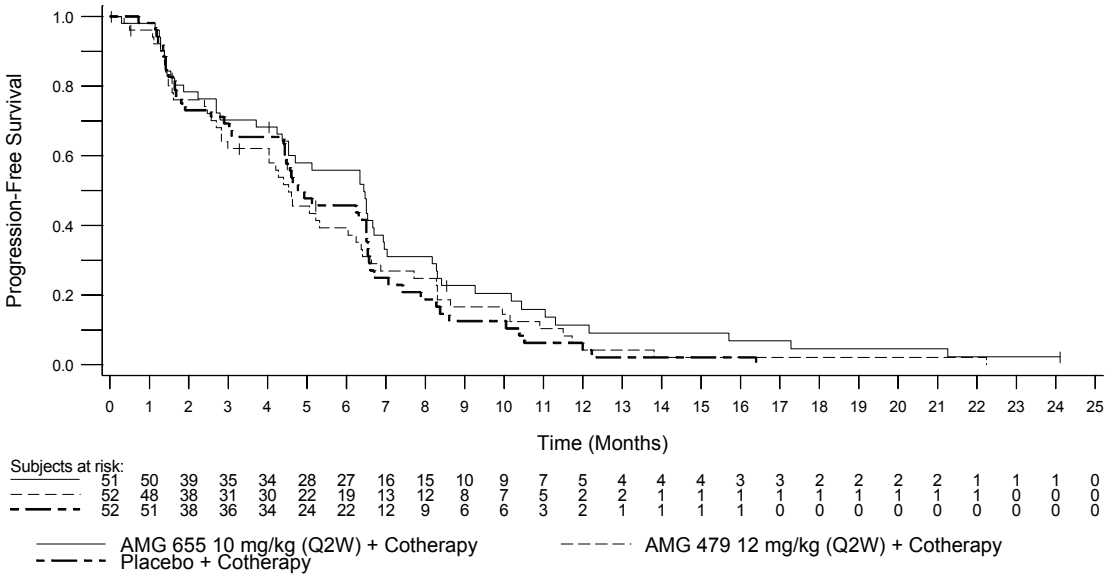
In the final analysis, per investigator review, 49 (94%) subjects in the ganitumab treatment arm and 50 (96%) subjects in the placebo treatment arm experienced PFS events (clinical progression, radiological progression, or death) (Table 14-4.3, FA). The median PFS time was 4.5 months for ganitumab versus 4.8 months for placebo. The hazard ratio (95% CI) at the final analysis, stratified by ECOG performance status (0 versus 1) and prior anti-VEGF exposure (yes versus no), was 1.11 (0.73, 1.67) for ganitumab compared with placebo, with a p-value of 0.632. Table 2 compares the PFS results from the primary analysis with those from the final analysis. The final Kaplan-Meier plot for PFS is provided in Figure 1.

Table 2. Analysis of Progression-free Survival – Ganitumab (Full Analysis Set)

	Primary Analysis		Final Analysis	
	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52)	Placebo + Cotherapy (N = 52)	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52)	Placebo + Cotherapy (N = 52)
Censored - n (%)	18 (35)	16 (31)	3 (6)	2 (4)
Events[a] - n (%)	34 (65)	36 (69)	49 (94)	50 (96)
Progression-free survival[b] (months)				
Median (K-M)	4.5	4.6	4.5	4.8
80% CI (K-M)	4.0, 5.3	4.4, 5.1	4.0, 5.3	4.5, 6.5
95% CI (K-M)	3.0, 6.6	3.1, 6.5	2.8, 6.2	4.4, 6.5
Q1, Q3 (K-M)	2.5, 8.3	1.8, 6.6	2.4, 7.7	1.9, 6.7
Min, Max	0.0, 11.7	0.0, 12.2	0.0, 22.2	0.7, 16.4
Stratified hazard ratio[c,d]	1.01		1.11	
80% CI	(0.73, 1.40)		(0.84, 1.45)	
95% CI	(0.61, 1.66)		(0.73, 1.67)	
Unstratified hazard ratio[c]	0.98		0.98	
80% CI	(0.72, 1.34)		(0.75, 1.27)	
95% CI	(0.61, 1.59)		(0.66, 1.46)	
Stratified log-rank test				
Normal score	0.003		0.479	
p-value[d,e]	0.998		0.632	
Unstratified log-rank test				
Normal score	-0.070		-0.106	
p-value[e]	0.944		0.916	

Note: The cotherapy is FOLFIRI.
Q2W = every 2 weeks; K-M = Kaplan-Meier estimate; CI = confidence interval; Min = minimum; Max = maximum; RECIST = Response Evaluation Criteria in Solid Tumors; ECOG = Eastern Cooperative Oncology Group; VEGF = vascular endothelial growth factor.
[a] Events are clinical progressions, radiological progressions, or deaths.
[b] Progression-free survival time is calculated as the number of days from randomization to the first assessment of disease progression (as classified by modified RECIST or clinical progression) or death due to any cause, divided by (365.25/12).
[c] The hazard ratio is obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer progression-free survival time for AMG 479 relative to placebo.
[d] Stratification factor is per primary pooling strategy: ECOG performance status (0 or 1) and prior anti-VEGF exposure (yes or no).
[e] A normal score < 0 indicates fewer than expected events for AMG 479 relative to placebo and, therefore, a longer progression-free survival time.
Source: Table 14-4.1 (Primary analysis); Table 14-4.3 (Final analysis)

Figure 1. Kaplan-Meier Plot of Progression-free Survival per Investigator Review (Full Analysis Set)



Program: /statistics/amg655/crc/20060579/analysis/part2_final/graphs/g_kmplot_eff.sas
Output: g14-04_002_km_pfs.cgm (Date Generated: 21AUG12:11:01:51) Source Data: adam.asleff

The final analysis piecewise model for PFS using a cutoff point of 3 months (0 to 3 and > 3 months) showed the following (Table 14-4.4, FA):

- For the time period of 0 to 3 months (19 [37%] subjects with events in the ganitumab treatment arm and 16 [31%] subjects with events in the placebo treatment arm): an unstratified hazard ratio (95% CI) of 1.27 (0.65, 2.47)
- For the time period of > 3 months (30 [58%] subjects with events in the ganitumab treatment arm and 34 [65%] subjects with events in the placebo treatment arm): an unstratified hazard ratio (95% CI) of 0.84 (0.51, 1.39)

Overall Survival

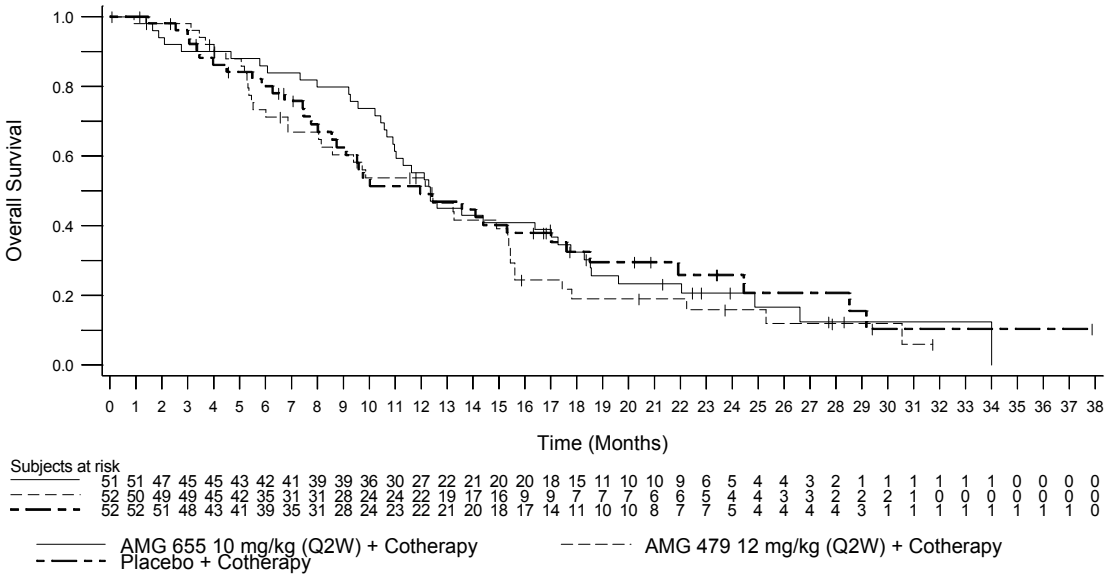
In the final analysis of OS, the data were more mature than in the primary analysis of OS. As of the final analysis, 39 (75%) subjects in the ganitumab treatment arm and 36 (69%) subjects in the placebo treatment arm had died (Table 14-4.1, FA). The median OS was 12.4 months for ganitumab and 12.0 months for placebo; the hazard ratio (95% CI), stratified by ECOG status of 0 or 1 and prior anti-VEGF exposure (yes versus no), was 1.27 (0.78, 2.06) for ganitumab compared with placebo, with a p-value of 0.342. Overall survival results from the primary analysis are compared with those of the final analysis in Table 3 and show that the median OS times for ganitumab and placebo at the final analysis were more similar to each other, numerically, than at the primary analysis. The final Kaplan-Meier plot for OS is provided in Figure 2.

Table 3. Analysis of Overall Survival – Ganitumab (Full Analysis Set)

	Primary Analysis		Final Analysis	
	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52)	Placebo + Cotherapy (N = 52)	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52)	Placebo + Cotherapy (N = 52)
Censored - n (%)	36 (69)	34 (65)	13 (25)	16 (31)
Events[a] - n (%)	16 (31)	18 (35)	39 (75)	36 (69)
Overall survival[b] (months)				
Median (K-M)	12.2	9.6	12.4	12.0
80% CI (K-M)	9.9, NE	8.7, 15.3	9.4, 14.9	9.5, 14.4
95% CI (K-M)	8.6, NE	8.0, NE	8.0, 15.4	8.5, 17.0
Q1, Q3 (K-M)	6.0, NE	6.7, NE	5.5, 15.6	7.4, 24.4
Min, Max	0.0, 15.1	0.1, 20.2	0.1, 31.7	1.5, 37.9
Stratified hazard ratio[c,d]	–		1.27	
80% CI			(0.92, 1.74)	
95% CI	–		(0.78, 2.06)	
Unstratified hazard ratio[c]	0.92		1.18	
80% CI	(0.59, 1.45)		(0.88, 1.59)	
95% CI	(0.46, 1.84)		(0.75, 1.87)	
Stratified log-rank test	–			
Normal score			0.950	
p-value[d, e]			0.342	
Unstratified log-rank test				
Normal score	-0.225		0.717	
p-value[e]	0.822		0.473	

Note: The cotherapy is FOLFIRI.
Q2W = every 2 weeks; K-M = Kaplan-Meier estimate; CI = confidence interval. NE = not estimable; Min = minimum; Max = maximum; - = data not available in primary report for comparisons; ECOG = Eastern Cooperative Oncology Group; VEGF = vascular endothelial growth factor.
[a] Events are deaths.
[b] Overall survival time is calculated as the number of days from randomization to to death due to any cause, divided by (365.25/12).
[c] The hazard ratio is obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer overall survival time for AMG 479 relative to placebo.
[d] Stratification factors are per primary pooling strategy: ECOG performance status (0 or 1) and prior anti-VEGF exposure (yes or no).
[e] A normal score < 0 indicates fewer than expected events for AMG 479 relative to placebo and, therefore, a longer overall survival time.
Source: Table 14-4.20 (Primary analysis); Table 14-4.1 (Final analysis)

Figure 2. Kaplan-Meier Plot of Overall Survival (Full Analysis Set)



Program: /statistics/amg655/crc/20060579/analysis/part2_final/graphs/g_kmplot_eff.sas
Output: g14-04_001_km_os.cgm (Date Generated: 21AUG12:11:01:26) Source Data: adam.asleff

The piecewise model for OS using a cutoff point of 6 months (0 to 6 and > 6 months) showed the following (Table 14-4.2, FA):

- For the time period of 0 to 6 months (13 [25%] subjects with events in the ganitumab treatment arm and 10 [19%] subjects with events in the placebo treatment arm): an unstratified hazard ratio (95% CI) of 1.32 (0.58, 3.01)
- For the time period of > 6 months (26 [50%] subjects with events in both treatment arms): an unstratified hazard ratio (95% CI) of 1.13 (0.65, 1.95)

Conatumumab

Progression-free Survival

In the final analysis, per investigator review, 47 (92%) subjects in the conatumumab treatment arm and 50 (96%) subjects in the placebo treatment arm experienced PFS events (clinical progression, radiological progression, or death) (Table 14-4.3, FA). The median PFS time was 6.4 months for conatumumab versus 4.8 months for placebo. The hazard ratio (95% CI) at the final analysis, stratified by ECOG performance status (0 versus 1) and prior anti-VEGF exposure (yes versus no), was 0.75 (0.49, 1.14) for conatumumab compared with placebo, with a p-value of 0.177, which was consistent with that of the primary analysis. Table 4 compares the PFS results from the primary analysis with those from the final analysis. The final Kaplan-Meier plot for PFS is provided in Figure 1.

Table 4. Analysis of Progression-free Survival – Conatumumab (Full Analysis Set)

	Primary Analysis		Final Analysis	
	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 52)	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 52)
Censored - n (%)	18 (35)	16 (31)	4 (8)	2 (4)
Events[a] - n (%)	33 (65)	36 (69)	47 (92)	50 (96)
Progression-free survival[b] (months)				
Median (K-M)	6.5	4.6	6.4	4.8
80% CI (K-M)	4.7, 6.7	4.4, 5.1	4.7, 6.7	4.5, 6.5
95% CI (K-M)	4.4, 7.0	3.1, 6.5	4.4, 6.9	4.4, 6.5
Q1, Q3 (K-M)	2.7, 8.3	1.8, 6.6	2.7, 8.3	1.9, 6.7
Min, Max	0.0, 21.3	0.0, 12.2	0.3, 24.1	0.7, 16.4
Stratified hazard ratio[c,d]	0.69		0.75	
80% CI	(0.49, 0.96)		(0.57, 0.99)	
95% CI	(0.41, 1.14)		(0.49, 1.14)	
Unstratified hazard ratio[c]	0.73		0.73	
80% CI	(0.53, 1.00)		(0.56, 0.96)	
95% CI	(0.45, 1.18)		(0.49, 1.10)	
Stratified log-rank test				
Normal score	-1.452		-1.350	
p-value[d,e]	0.147		0.177	
Unstratified log-rank test				
Normal score	-1.293		-1.488	
p-value[e]	0.196		0.137	

Note: The cotherapy is FOLFIRI.
Q2W = every 2 weeks; K-M = Kaplan-Meier estimate; CI = confidence interval; Min = minimum; Max = maximum; RECIST = Response Evaluation Criteria in Solid Tumors; ECOG = Eastern Cooperative Oncology Group; VEGF = vascular endothelial growth factor.
[a] Events are clinical progressions, radiological progressions, or deaths.
[b] Progression-free survival time is calculated as the number of days from randomization to the first assessment of disease progression (as classified by modified RECIST or clinical progression) or death due to any cause, divided by (365.25/12).
[c] The hazard ratio is obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer progression-free survival time for AMG 655 relative to placebo.
[d] Stratification factor is per primary pooling strategy: ECOG performance status (0 or 1) and prior anti-VEGF exposure (yes or no).
[e] A normal score < 0 indicates fewer than expected events for AMG 655 relative to placebo and, therefore, a longer progression-free survival time.
Source: Table 14-4.1 (Primary analysis); Table 14-4.3 (Final analysis)

The final analysis piecewise model for PFS using a cutoff point of 3 months (0 to 3 and > 3 months) showed the following (Table 14-4.4, FA):

- For the time period of 0 to 3 months (15 [29%] subjects with events in the conatumumab treatment arm and 16 [31%] subjects with events in the placebo treatment arm): an unstratified hazard ratio (95% CI) of 0.95 (0.47, 1.92)
- For the time period of > 3 months (32 [63%] subjects with events in the conatumumab treatment arm and 34 [65%] subjects with events in the placebo treatment arm): an unstratified hazard ratio (95% CI) of 0.65 (0.39, 1.06)

Overall Survival

In the final analysis of OS, the data were more mature than in the primary analysis of OS. As of the final analysis, 41 (80%) subjects in the conatumumab treatment arm and 36 (69%) subjects in the placebo treatment arm had died (Table 14-4.1, FA). The median OS was 12.4 months for conatumumab and 12.0 months for placebo; the hazard ratio (95% CI), stratified by ECOG status of 0 or 1 and prior anti-VEGF exposure (yes versus no), was 0.96 (0.61, 1.53) for conatumumab compared with placebo, with a p-value of 0.867. Overall survival results from the primary analysis are compared with those of the final analysis in Table 5 and show that the median OS times for conatumumab and placebo at the final analysis were closer, numerically, than at the primary analysis. The final Kaplan-Meier plot for OS is provided in Figure 2.

Table 5. Analysis of Overall Survival – Conatumumab (Full Analysis Set)

	Primary Analysis		Final Analysis	
	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 52)	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 52)
Censored - n (%)	34 (67)	34 (65)	10 (20)	16 (31)
Events[a] - n (%)	17 (33)	18 (35)	41 (80)	36 (69)
Overall survival[b] (months)				
Median (K-M)	12.3	9.6	12.4	12.0
80% CI (K-M)	10.6, 12.4	8.7, 15.3	11.0, 14.4	9.5, 14.4
95% CI (K-M)	10.4, 17.3	8.0, NE	10.9, 17.0	8.5, 17.0
Q1, Q3 (K-M)	10.2, 17.3	6.7, NE	9.6, 19.6	7.4, 24.4
Min, Max	0.0, 22.4	0.1, 20.2	1.1, 34.0	1.5, 37.9
Stratified hazard ratio[c,d]	–		0.96	
80% CI			(0.71, 1.30)	
95% CI	–		(0.61, 1.53)	
Unstratified hazard ratio[c]	0.84		1.00	
80% CI	(0.54, 1.30)		(0.75, 1.35)	
95% CI	(0.43, 1.64)		(0.64, 1.58)	
Stratified log-rank test	–			
Normal score			-0.167	
p-value[d, e]			0.867	
Unstratified log-rank test				
Normal score	-0.509		0.014	
p-value[e]	0.610		0.989	

Note: The cotherapy is FOLFIRI.
Q2W = every 2 weeks; K-M = Kaplan-Meier estimate; CI = confidence interval. NE = not estimable; Min = minimum; Max = maximum; - = data not available in primary report for comparisons; ECOG = Eastern Cooperative Oncology Group; VEGF = vascular endothelial growth factor.
[a] Events are deaths.
[b] Overall survival time is calculated as the number of days from randomization to to death due to any cause, divided by (365.25/12).
[c] The hazard ratio is obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer overall survival time for AMG 655 relative to placebo.
[d] Stratification factor is per primary pooling strategy: ECOG performance status (0 or 1) and prior anti-VEGF exposure (yes or no).
[e] A normal score < 0 indicates fewer than expected events for AMG 655 relative to placebo and, therefore, a longer overall survival time.
Source: Table 14-4.20 (Primary analysis); Table 14-4.1 (Final analysis)

The piecewise model for OS using a cutoff point of 6 months (0 to 6 and > 6 months) showed the following (Table 14-4.2, FA):

- For the time period of 0 to 6 months (7 [14%] subjects with events in the conatumumab treatment arm and 10 [19%] subjects with events in the placebo treatment arm): an unstratified hazard ratio (95% CI) of 0.71 (0.27, 1.87)
- For the time period of > 6 months (34 [67%] subjects with events in the conatumumab treatment arm and 26 [50%] subjects in the placebo treatment arm): an unstratified hazard ratio (95% CI) of 1.11 (0.66, 1.85)

Safety Results:

Extent of exposure and safety data are summarized separately for ganitumab and conatumumab below.

Ganitumab

Extent of Exposure

As of the final analysis, subjects in the ganitumab treatment arm received a median of 13 infusions (range: 2 to 60) of investigational product compared with a median of 18 infusions (range: 2 to 54) in subjects in the placebo treatment arm (Table 14-5.1, FA). The median number of months on treatment for subjects in the ganitumab and placebo treatment arms was 4.2 and 4.9, respectively; the median average ganitumab dose delivered to subjects was 12.00 mg/kg/infusion; and the median relative dose intensity was 0.96 for ganitumab. Investigational product dose modifications made in the ganitumab and placebo treatment arms were as follows (Table 14-5.6, FA):

- At least 1 dose change (and most common reason for the change): ganitumab: 7 subjects, 13% (weight change, 4 subjects, 8%); placebo: 11 subjects, 22% (weight change, 5 subjects, 10%)
- At least 1 dose delay (and most common reason for delay): ganitumab: 25 subjects, 48% (protocol-specified adverse event, 12 subjects, 23%); placebo: 27 subjects, 53% (“other,” 16 subjects, 31%)
- At least 1 dose withheld (and most common reason for withholding): ganitumab: 9 subjects, 17% (adverse event, 5 subjects, 10%); placebo: 9 subjects, 18% (adverse event and “other,” 5 subjects, 10% each)

Extent of exposure to the cotherapies in the ganitumab and placebo treatment arms at the time of the final analysis was as follows (Table 14-5.2, FA through Table 14-5.5, FA):

- Leucovorin: median number of infusions was 5.5 (range: 0 to 30) and 10.0 (range: 1 to 27), respectively; median number of months on treatment was 3.7 and 4.9; median average dose delivered was 200.73 and 199.61 mg/m^2/infusion; and median relative dose intensity was 0.93 and 0.89
- Irinotecan: median number of infusions was 6.0 (range: 0 to 30) and 10.0 (range: 1 to 27), respectively; median number of months on treatment was 4.2 and 4.9; median average dose delivered was 176.05 and 176.09 mg/m^2/infusion; and median relative dose intensity was 0.92 and 0.91
- 5-FU bolus: median number of infusions was 5.5 (range: 1 to 30) and 9.0 (range: 1 to 27), respectively; median number of months on treatment was 3.7 and 4.9; median average dose delivered was 389.67 and 388.93 mg/m^2/infusion; and median relative dose intensity was 0.89 and 0.83
- 5-FU continuous IV Infusion: median number of infusions was 5.0 (range: 1 to 30) and 10.0 (range: 1 to 27), respectively; median number of months on treatment was 3.7 and 4.9; median average dose delivered was 2333.27 and 2333.58 mg/m^2/infusion; and median relative dose intensity was 0.88 and 0.86

Cotherapy dose modifications are summarized in Table 14-5.7, FA through Table 14-5.10, FA.

Safety Results

All Treatment-emergent Adverse Events

Based on final analysis results, the overall percentage of subjects reporting at least 1 treatment-emergent adverse event was comparable between the 2 treatment arms: ganitumab: 94%; placebo: 98% (Table 14-6.4, FA). Table 6 presents the treatment-emergent adverse events reported most frequently (≥ 10% of subjects in either treatment arm) and compares the primary analysis results with the final analysis results.

In the final analysis, the adverse event reported in more than half of the subjects in the ganitumab treatment arm was neutropenia (ganitumab: 52%; placebo: 41%). Adverse events in Table 6 that were reported in ≥ 5% more subjects in the ganitumab arm than in the placebo arm included neutropenia (52%, 41%, respectively), anemia (27%, 16%), thrombocytopenia (23%, 6%), leukopenia (15%, 4%), and chills (13%, 6%). Results from the primary analysis were generally consistent with those in the final analysis.

Table 6. Most Frequently Reported (≥ 10%) Treatment-emergent Adverse Events (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Preferred Term	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 51)	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52)	Placebo + Cotherapy (N = 51)
Subjects reporting at least 1 adverse event	47 (92)	49 (96)	49 (94)	50 (98)
Neutropenia	24 (47)	19 (37)	27 (52)	21 (41)
Diarrhoea	22 (43)	21 (41)	23 (44)	23 (45)
Nausea	18 (35)	17 (33)	19 (37)	20 (39)
Vomiting	14 (27)	14 (27)	15 (29)	14 (27)
Fatigue	15 (29)	11 (22)	15 (29)	13 (25)
Anaemia	14 (27)	5 (10)	14 (27)	8 (16)
Thrombocytopenia	12 (24)	3 (6)	12 (23)	3 (6)
Alopecia	9 (18)	11 (22)	11 (21)	13 (25)
Constipation	7 (14)	17 (33)	10 (19)	19 (37)
Stomatitis	10 (20)	10 (20)	10 (19)	11 (22)
Abdominal pain	9 (18)	8 (16)	10 (19)	10 (20)
Decreased appetite	10 (20)	8 (16)	10 (19)	9 (18)
Asthenia	8 (16)	12 (24)	8 (15)	14 (27)
Pyrexia	8 (16)	5 (10)	8 (15)	8 (16)
Leukopenia	8 (16)	1 (2)	8 (15)	2 (4)
Back pain	3 (6)	5 (10)	6 (12)	8 (16)
Dizziness	5 (10)	4 (8)	6 (12)	4 (8)
Chills	7 (14)	3 (6)	7 (13)	3 (6)
Epistaxis	4 (8)	3 (6)	5 (10)	3 (6)
Abdominal pain upper	3 (6)	5 (10)	4 (8)	5 (10)
Intestinal obstruction	3 (6)	4 (8)	4 (8)	5 (10)
Hyperglycaemia	5 (10)	3 (6)	4 (8)	5 (10)
Headache	3 (6)	6 (12)	3 (6)	7 (14)
Mucosal inflammation	2 (4)	7 (14)	2 (4)	10 (20)
Hypokalaemia	2 (4)	4 (8)	2 (4)	5 (10)
Dry skin	2 (4)	2 (4)	2 (4)	5 (10)
Anxiety	2 (4)	4 (8)	2 (4)	5 (10)
Pain	2 (4)	5 (10)	2 (4)	5 (10)
Oedema peripheral	1 (2)	5 (10)	1 (2)	7 (14)

Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using Common Terminology Criteria for Adverse Events (CTCAE).
Source: Table 14-6.4 (Primary analysis); Table 14-6.4 (Final analysis)

Treatment-emergent adverse events that were considered by the investigator to be related to investigational product or chemotherapy administration were reported in 83% of subjects in the ganitumab treatment arm and 90% of subjects in the placebo treatment arm (Table 14-6.5, FA). The most frequently reported treatment-related adverse events (≥ 20% of subjects in either treatment arm) were generally consistent with those reported most frequently in the all-treatment-emergent-adverse-event presentation: neutropenia (ganitumab: 48%; placebo: 39%), diarrhea (40%; 39%), nausea (33%; 37%), vomiting (23%; 24%), fatigue (21%; 22%), anemia (21%; 12%), thrombocytopenia (21%; 6%), alopecia (17%; 25%), asthenia (12%; 22%), and stomatitis (17%; 20%).

Grade ≥ 3 Treatment-emergent Adverse Events

The overall incidence of grade ≥ 3 treatment-emergent adverse events in the final analysis was 65% for ganitumab and 57% for placebo (Table 14-6.9, FA). Those reported in ≥ 10% of subjects in either treatment arm included neutropenia (ganitumab: 33%; placebo: 22%), intestinal obstruction (8%; 10%), and diarrhea (2%; 12%). The grade ≥ 3 adverse event of neutropenia was reported in more than 5% more subjects in the ganitumab treatment arm (33%) than the placebo treatment arm (22%); all other events were reported at similar frequencies except diarrhea, which was reported in 2% of subjects for ganitumab versus 12% of subjects for placebo. Table 7 summarizes the most frequently reported grade ≥ 3 treatment-emergent adverse events from both the primary analysis and the final analysis.

Table 7. Most Frequently Reported (≥ 5%) Grade 3, 4, and 5 Treatment-emergent Adverse Events (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Preferred Term	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 51)	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52)	Placebo + Cotherapy (N = 51)
Subjects reporting at least 1 grade 3, 4, or 5 adverse event	28 (55)	24 (47)	34 (65)	29 (57)
Neutropenia	13 (25)	9 (18)	17 (33)	11 (22)
Anaemia	4 (8)	2 (4)	4 (8)	3 (6)
Intestinal obstruction	3 (6)	4 (8)	4 (8)	5 (10)
Abdominal pain	2 (4)	2 (4)	3 (6)	2 (4)
Leukopenia	3 (6)	0 (0)	3 (6)	0 (0)
Hyperglycaemia	4 (8)	2 (4)	3 (6)	3 (6)
Vomiting	1 (2)	3 (6)	2 (4)	3 (6)
Asthenia	1 (2)	3 (6)	2 (4)	3 (6)
Diarrhoea	1 (2)	5 (10)	1 (2)	6 (12)
Fatigue	1 (2)	2 (4)	1 (2)	3 (6)
Mucosal inflammation	0 (0)	2 (4)	0 (0)	3 (6)

Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using CTCAE.
Source: Table 14-6.13 (Primary analysis); Table 14-6.9 (Final analysis)

Serious Treatment-emergent Adverse Events

As of the final analysis, the overall incidence of treatment-emergent serious adverse events was comparable between the ganitumab and placebo treatment arms (33% and 31%, respectively) (Table 14-6.14, FA). The frequencies were similar between the ganitumab and placebo treatment arms for each of the serious adverse events. The events reported in ≥ 5% of subjects in either treatment arm were diarrhea (2% and 6%, respectively) and intestinal obstruction (8%, 6%). Table 8 summarizes the serious adverse events reported in ≥ 5% of subjects in either treatment arm from the primary analysis and the final analysis.

Detailed narratives for subjects with serious adverse events reported throughout the study are provided in Appendix 5.

Table 8. Most Frequently Reported (≥ 5%) Treatment-emergent Serious Adverse Events (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Preferred Term	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 51)	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52)	Placebo + Cotherapy (N = 51)
Subjects reporting at least 1 serious adverse event	16 (31)	12 (24)	17 (33)	16 (31)
Diarrhoea	1 (2)	3 (6)	1 (2)	3 (6)
Intestinal obstruction	3 (6)	2 (4)	4 (8)	3 (6)

Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using CTCAE.
Source: Table 14-6.14 (Primary analysis); Table 14-6.14 (Final analysis)

Deaths

At the final analysis, a total of 39 (75%) subjects in the ganitumab treatment arm and 36 (71%) subjects in the placebo treatment arm died in the study (Listing 14-6.2, FA), which represents an additional 23 deaths and 18 deaths, respectively, since the primary analysis (Table 14-6.45, PA). For most of these subjects, overall, the primary cause of death was disease progression.

As of the final analysis, the deaths for 3 subjects in the ganitumab treatment arm resulted from the treatment-emergent adverse events of rectal cancer, diabetic ketoacidosis, and intestinal obstruction (this event reported after the primary analysis). None of these events were considered to be related to either investigational product or chemotherapy. No subjects in the placebo treatment arm died from a treatment-emergent adverse event.

Detailed narratives for subjects with fatal adverse events reported throughout the study are provided in Appendix 5.

Treatment-emergent Adverse Events Leading to Study Withdrawal or Discontinuation of Therapy

At the time of the final analysis, the incidence of treatment-emergent adverse events in the ganitumab (4% [2 subjects]) and placebo (2% [1 subject]) treatment arms leading to withdrawal from the study was unchanged from the primary analysis (Table 14-6.15, PA; Table 14-6.1, FA). For ganitumab, the events included grade 4 acute cholangitis (serious adverse event) and grade 1 thrombocytopenia (nonserious); for placebo, the event was grade 3 metastases to central nervous system (serious) (Listing 14-6.3, FA).

The summary of treatment-emergent adverse events leading to discontinuation of investigational product at the final analysis changed little from the primary analysis: 7 (13%) subjects in the ganitumab treatment arm (the same number of subjects as in the primary analysis) and 5 (10%) subjects in the placebo treatment arm (1 additional subject since the primary analysis) (Table 14-6.45, FA). Adverse events leading to discontinuation of investigational product in the ganitumab arm included thrombocytopenia, keratitis, colonic obstruction, intestinal obstruction, cholangitis acute, hyperbilirubinemia, alanine aminotransferase (ALT) increased, and diabetic ketoacidosis; in the placebo arm, these events included pancytopenia, cardiac failure congestive, abdominal pain, diarrhea, and metastases to central nervous system.

As of the final analysis, treatment-emergent adverse events leading to discontinuation of all protocol-specified therapy occurred in 5 (10%) subjects in the ganitumab treatment arm and 3 (6%) subjects in the placebo treatment arm; these results represent little change from the primary analysis (Listing 14-6.8, PA; Table 14-6.46, FA). The adverse events leading to discontinuation of all protocol-specified therapy in the ganitumab treatment arm were intestinal obstruction, keratitis, colonic obstruction, acute cholangitis, and thrombocytopenia (the events of acute cholangitis and thrombocytopenia also led to withdrawal from the study); the events leading to discontinuation of all protocol-specified therapy in the placebo treatment arm were diarrhea, congestive cardiac failure, and pancytopenia.

Adverse Events of Interest

Adverse events of interest for ganitumab include hyperglycemia, thrombocytopenia, hepatic disorders, rash, infusion reaction, neutropenia, venous thromboembolic events, and sensorineural hearing loss. Search strategies using broad and narrow search terms were implemented at both the primary and final analyses; for this clinical study report, the focus is on the output using the narrow search strategy for each event of interest.

By the time of the final analysis, the overall frequency of adverse events of interest was comparable between the ganitumab and placebo treatment arms (65% each) (Table 14-6.47, FA). Neutropenia and thrombocytopenia were reported most often in the ganitumab arm at the final analysis, and they occurred at higher frequencies in the ganitumab arm than the placebo arm (neutropenia: 52%, 41%, respectively; thrombocytopenia: 23%, 6%). Hepatic disorders, venous thromboembolic events, sensorineural hearing loss, and hyperglycemia occurred at generally similar frequencies in the 2 treatment arms. Adverse events of interest that were grade ≥ 3 occurred in ≤ 2 subjects in each event of interest except for neutropenia, of which 33% of subjects in the ganitumab treatment arm and 22% of subjects in the placebo treatment arm reported such events. A medical review was also performed of the broad search terms for the drug-related hepatic disorders event of interest, which revealed a grade 3 event of hypoalbuminemia in the ganitumab arm (Table 14-6.17, FA).

An overview of the adverse events of interest from the primary analysis and the final analysis (narrow terms) is provided in Table 9.

Table 9. Incidence of Treatment-emergent Adverse Events of Interest Narrow Search Terms (Safety Analysis Set)

	Primary Analysis				Final Analysis			
Event of Interest Category	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 51) n (%)		Placebo + Cotherapy (N = 51) n (%)		AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52) n (%)		Placebo + Cotherapy (N = 51) n (%)	
Subjects reporting any adverse event of interest	33 (65)		28 (55)		34 (65)		33 (65)	
	Total	Grade ≥ 3	Total	Grade ≥ 3	Total	Grade ≥ 3	Total	Grade ≥ 3
Drug-related hepatic disorders	7 (14)	2 (4)	4 (8)	1 (2)	7 (13)	2 (4)	6 (12)	1 (2)
Venous thromboembolic events	2 (4)	2 (4)	1 (2)	1 (2)	2 (4)	2 (4)	3 (6)	2 (4)
Sensorineural hearing loss	3 (6)	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	1 (2)	0 (0)
Hyperglycaemia	5 (10)	3 (6)	3 (6)	2 (4)	4 (8)	2 (4)	5 (10)	3 (6)
Infusion reaction	5 (10)	0 (0)	3 (6)	0 (0)	5 (10)	0 (0)	3 (6)	0 (0)
Treatment-related infusion reaction	5 (10)	0 (0)	1 (2)	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)
Neutropenia	26 (51)	15 (29)	19 (37)	9 (18)	27 (52)	17 (33)	21 (41)	11 (22)
Rash	2 (4)	0 (0)	7 (14)	0 (0)	2 (4)	0 (0)	8 (16)	0 (0)
Thrombocytopenia	12 (24)	1 (2)	3 (6)	0 (0)	12 (23)	1 (2)	3 (6)	0 (0)

Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using CTCAE.
Source: Table 14-6.60 (Primary analysis); Table 14-6.47 (Final analysis)

Clinical Laboratory Evaluations

The incidence of treatment-emergent grade ≥ 3 chemistry and hematology laboratory values as of the final analysis was similar between the ganitumab and placebo treatment arms for most of the analytes; those analytes with a higher incidence of grade ≥ 3 treatment-emergent values (≥ 5%) in the ganitumab arm versus placebo included alkaline phosphatase (12% and 6%, respectively [all were elevated values]), lipase (10%, 4% [all elevated values]), and sodium (10%, 2% [all decreased values]) for chemistry and absolute neutrophil count (31%, 24% [all decreased values]) for hematology, The only analyte with a higher incidence of grade ≥ 3 treatment-emergent values (≥ 5%) in the placebo arm versus the ganitumab arm was potassium (8%, 2%, respectively [decreased values with the exception of 1 elevated value in the placebo arm]) (Table 14-7.2, FA; Listing 14-7.1, FA; Listing 14-7.2, FA).

Table 10 presents the frequencies of grade ≥ 3 chemistry and hematology values for the primary analysis compared with the final analysis. The results were generally consistent between the 2 analyses, with the exception of a decrease in grade ≥ 3 lymphocytes in the ganitumab arm between the primary (18%) and the final (10%) analysis.

Change from baseline in chemistry analytes for the final analysis are summarized in Table 14-7.6, FA through Table 14-7.16, FA and Table 14-7.18, FA through Table 14-7.24, FA. Change from baseline in hematology analytes for the final analysis are summarized in Table 14-7.17, FA and Table 14-7.25, FA through Table 14-7.37, FA.

Table 10. Incidence of Treatment-emergent NCI CTCAE Grade ≥ 3 (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Category Analyte	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 51)	AMG 479 12 mg/kg (Q2W) + Cotherapy (N = 52)	Placebo + Cotherapy (N = 51)
Chemistry				
ALT	2 (4)	0 (0)	2 (4)	0 (0)
Albumin	1 (2)	0 (0)	1 (2)	0 (0)
Alkaline phosphatase	5 (10)	2 (4)	6 (12)	3 (6)
Amylase	0 (0)	0 (0)	0 (0)	0 (0)
AST	2 (4)	0 (0)	2 (4)	1 (2)
Bicarbonate	1 (2)	0 (0)	1 (2)	0 (0)
Calcium	2 (4)	0 (0)	2 (4)	0 (0)
Glucose	4 (8)	3 (6)	4 (8)	3 (6)
Lipase	5 (10)	2 (4)	5 (10)	2 (4)
Magnesium	0 (0)	0 (0)	0 (0)	0 (0)
Phosphorus	1 (2)	0 (0)	1 (2)	1 (2)
Potassium	1 (2)	2 (4)	1 (2)	4 (8)
Sodium	5 (10)	0 (0)	5 (10)	1 (2)
Total bilirubin	1 (2)	1 (2)	1 (2)	1 (2)
Hematology				
Absolute neutrophil count	14 (27)	10 (20)	16 (31)	12 (24)
Hemoglobin	3 (6)	2 (4)	4 (8)	3 (6)
Lymphocytes	9 (18)	3 (6)	5 (10)	4 (8)
Platelets	3 (6)	1 (2)	3 (6)	1 (2)
White blood cells	6 (12)	4 (8)	6 (12)	4 (8)

Note: The cotherapy is FOLFIRI.
Note: Based on NCI-CTCAE version 3.0.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI = National Cancer Institute; CTCAE = Common Terminology Criteria for Adverse Events.
Source: Table 14-7.79 and Table 14-7.80 (Primary analysis); Table 14-7.2 (Final analysis)

At the final analysis, 1 subject in the ganitumab treatment arm (Subject [redacted]) exhibited liver analyte abnormalities that met the criteria for Hy's Law (ALT or aspartate aminotransferase [AST] ≥ 3 x the upper limit of normal [ULN], total bilirubin > 2 x ULN, and alkaline phosphatase ≤ 2 x ULN) (Table 14-7.40, FA; Listing 14-7.3, FA). No subjects in the placebo treatment group met these criteria. Subject [redacted], a [redacted], had a prior medical history of hepatitis/toxic hepatitis and metastases to the liver and biliary tract (Listing 14.2.2, PA; Listing 14-4.2, PA). Values for ALT, AST, total bilirubin, and alkaline phosphatase each met the individual criteria at multiple time points during the study. The highest values (all grade 4) for ALT, AST, and total bilirubin for this subject occurred on study day 74 (1371 U/L, 669 U/L, and 277.0 µmol/L, respectively); on this day, alkaline phosphatase, at 559 U/L (grade 2), was also the highest value (not meeting Hy's Law criteria). Alkaline phosphatase was > 2 x ULN at most time points during the study. Multiple adverse events of ALT increased, AST increased, and hyperbilirubinemia were reported during the study, some of which were considered to be related to investigational product (Listing 14-6.4, FA). This subject discontinued treatment with ganitumab as a result of 2 events of ALT increased (considered related to investigational product) and hyperbilirubinemia (not related) on day 58. An event of hyperbilirubinemia was reported on day 66 (considered not related to investigational product) that met serious criteria; the following day, radiological disease progression was documented for this subject (Listing 14-1.7, PA). The last dose of ganitumab was administered on day 30 (cycle 2, day 1), and the last dose of the cotherapies was day 44. The subject died due to disease progression on day 198 (Listing 14-6.2, FA).

Conatumumab

Extent of Exposure

As of the final analysis, subjects in the conatumumab treatment arm received a median of 14 infusions (range: 2 to 92) of investigational product compared with a median of 18 infusions (range: 2 to 54) in subjects in the placebo treatment arm (Table 14-5.1, FA). The median number of months on treatment for subjects in the conatumumab and placebo treatment arms was 4.5 and 4.9, respectively; the median average conatumumab dose delivered to subjects was 10.00 mg/kg/infusion; and the median relative dose intensity was 0.88 for conatumumab. Investigational product dose modifications made in the conatumumab and placebo treatment arms were as follows (Table 14-5.6, FA):

- At least 1 dose change (and most common reason for the change): conatumumab: 13 subjects, 25% (adverse event and weight change, 5 subjects, 10% each); placebo: 11 subjects, 22% (weight change, 5 subjects, 10%)
- At least 1 dose delay (and most common reason for delay): conatumumab: 34 subjects, 67% ("other," 21 subjects, 41%); placebo: 27 subjects, 53% ("other," 16 subjects, 31%)
- At least 1 dose withheld (and most common reason for withholding): conatumumab: 10 subjects, 20% (adverse event, 6 subjects, 12%); placebo: 9 subjects, 18% (adverse event and "other," 5 subjects, 10% each)

Extent of exposure to the cotherapies in the conatumumab and placebo treatment arms at the time of the final analysis was as follows (Table 14-5.2, FA through Table 14-5.5, FA):

- Leucovorin: median number of infusions was 7.0 (range: 0 to 46) and 10.0 (range: 1 to 27), respectively; median number of months on treatment was 4.5 and 4.9; median average dose delivered was 200.26 and 199.61 mg/m^2/infusion; and median relative dose intensity was 0.85 and 0.89
- Irinotecan: median number of infusions was 7.0 (range: 1 to 46) and 10.0 (range: 1 to 27), respectively; median number of months on treatment was 4.5 and 4.9; median average dose delivered was 177.43 and 176.09 mg/m^2/infusion; and median relative dose intensity was 0.85 and 0.91
- 5-FU bolus: median number of infusions was 7.0 (range: 0 to 46) and 9.0 (range: 1 to 27), respectively; median number of months on treatment was 4.5 and 4.9; median

average dose delivered was 364.65 and 388.93 mg/m^2/infusion; and median relative dose intensity was 0.80 and 0.83

- 5-FU continuous IV Infusion: median number of infusions was 7.0 (range: 0 to 46) and 10.0 (range: 1 to 27), respectively; median number of months on treatment was 4.5 and 4.9; median average dose delivered was 2221.03 and 2333.58 mg/m^2/infusion; and median relative dose intensity was 0.81 and 0.86

Cotherapy dose modifications are summarized in Table 14-5.7, FA through Table 14-5.10, FA.

Safety Results

All Treatment-emergent Adverse Events

Based on final analysis results, the overall percentage of subjects reporting at least 1 treatment-emergent adverse event was the same (98%) in both the conatumumab and placebo treatment arms (Table 14-6.4, FA). Table 11 presents the treatment-emergent adverse events reported most frequently (≥ 10% of subjects in either treatment arm) and compares the primary analysis results with the final analysis results.

In the final analysis, adverse events reported in more than half of the subjects in the conatumumab treatment arm were neutropenia (conatumumab: 53%; placebo: 41%) and diarrhea (59%; 45%). Adverse events in Table 11 that were reported in ≥ 5% more subjects in the conatumumab arm than the placebo arm were diarrhea (59% and 45%, respectively) neutropenia (53%, 41%), anemia (24%, 16%), decreased appetite (24%, 18%), pyrexia (22%, 16%), rash (16%, 6%), chills (14%, 6%), dehydration (14%, 6%), peripheral neuropathy (14%, 2%), hypomagnesemia (12%, 2%), hypertension (10%, 2%), depression (10%, 2%), and urinary tract infection (10%, 0%). Results from the primary analysis were generally consistent with those from the final analysis.

Table 11. Most Frequently Reported (≥ 10%) Treatment-emergent Adverse Events (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Preferred Term	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 50)	Placebo + Cotherapy (N = 51)	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 51)
Subjects reporting at least 1 adverse event	48 (96)	49 (96)	50 (98)	50 (98)
Diarrhoea	29 (58)	21 (41)	30 (59)	23 (45)
Neutropenia	27 (54)	19 (37)	27 (53)	21 (41)
Nausea	18 (36)	17 (33)	19 (37)	20 (39)
Asthenia	15 (30)	12 (24)	16 (31)	14 (27)
Vomiting	14 (28)	14 (27)	14 (27)	14 (27)
Anaemia	10 (20)	5 (10)	12 (24)	8 (16)
Alopecia	13 (26)	11 (22)	12 (24)	13 (25)
Abdominal pain	12 (24)	8 (16)	12 (24)	10 (20)
Decreased appetite	12 (24)	8 (16)	12 (24)	9 (18)
Fatigue	11 (22)	11 (22)	11 (22)	13 (25)
Pyrexia	9 (18)	5 (10)	11 (22)	8 (16)
Mucosal inflammation	9 (18)	7 (14)	9 (18)	10 (20)
Rash	7 (14)	3 (6)	8 (16)	3 (6)
Constipation	8 (16)	17 (33)	7 (14)	19 (37)
Chills	7 (14)	3 (6)	7 (14)	3 (6)
Dehydration	7 (14)	2 (4)	7 (14)	3 (6)
Neuropathy peripheral	7 (14)	1 (2)	7 (14)	1 (2)
Hypokalaemia	6 (12)	4 (8)	6 (12)	5 (10)
Cough	6 (12)	3 (6)	6 (12)	4 (8)
Hypomagnesaemia	6 (12)	0 (0)	6 (12)	1 (2)
Stomatitis	4 (8)	10 (20)	5 (10)	11 (22)
Headache	5 (10)	6 (12)	5 (10)	7 (14)
Insomnia	5 (10)	4 (8)	5 (10)	4 (8)
Weight decreased	5 (10)	3 (6)	5 (10)	3 (6)
Dyspnoea	4 (8)	2 (4)	5 (10)	3 (6)
Hypertension	4 (8)	1 (2)	5 (10)	1 (2)

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Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using CTCAE.
Source: Table 14-6.4 (Primary analysis); Table 14-6.4 (Final analysis)

Table 11. Most Frequently Reported (≥ 10%) Treatment-emergent Adverse Events (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Preferred Term	AMG 655 10 mg/kg (Q2W) + Cotherapy (N=50)	Placebo + Cotherapy (N=51)	AMG 655 10 mg/kg (Q2W) + Cotherapy (N=51)	Placebo + Cotherapy (N=51)
Depression	5 (10)	0 (0)	5 (10)	1 (2)
Urinary tract infection	4 (8)	0 (0)	5 (10)	0 (0)
Abdominal pain upper	3 (6)	5 (10)	4 (8)	5 (10)
Back pain	3 (6)	5 (10)	3 (6)	8 (16)
Oedema peripheral	3 (6)	5 (10)	3 (6)	7 (14)
Intestinal obstruction	3 (6)	4 (8)	3 (6)	5 (10)
Pain	3 (6)	5 (10)	3 (6)	5 (10)
Anxiety	2 (4)	4 (8)	2 (4)	5 (10)
Hyperglycaemia	2 (4)	3 (6)	2 (4)	5 (10)
Dry skin	2 (4)	2 (4)	2 (4)	5 (10)

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Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using CTCAE.
Source: Table 14-6.4 (Primary analysis); Table 14-6.4 (Final analysis)

Treatment-emergent adverse events that were considered by the investigator to be related to investigational product or chemotherapy administration were reported in 88% of subjects in the conatumumab treatment arm and 90% of subjects in the placebo treatment arm (Table 14-6.5, FA). The most frequently reported treatment-related adverse events (≥ 20% of subjects in either treatment arm) were generally consistent with those reported most frequently in the all-treatment-emergent-adverse-event presentation: neutropenia (conatumumab: 51%; placebo: 39%), diarrhea (51%; 39%), nausea (35%; 37%), vomiting (24%; 24%), alopecia (24%; 25%), fatigue (22%; 22%), asthenia (25%; 22%), anemia (24%; 12%), decreased appetite (20%; 16%), and stomatitis (10%; 20%).

Grade ≥ 3 Treatment-emergent Adverse Events

The overall incidence of grade ≥ 3 treatment-emergent adverse events in the final analysis was 76% for conatumumab and 57% for placebo (Table 14-6.9, FA). Those reported in ≥ 10% of subjects in either treatment arm included neutropenia (conatumumab: 29%; placebo: 22%), diarrhea (20%; 12%), fatigue (10%; 6%), and intestinal obstruction (4%; 10%). Four grade ≥ 3 adverse events were reported in more than 5% more subjects in the conatumumab treatment arm than the placebo treatment arm: neutropenia (29% and 22%, respectively), diarrhea (20%, 12%), decreased appetite (8%, 0%), and weight decreased (6%, 0%); all other events were reported at similar frequencies except intestinal obstruction, which was reported in 4% of subjects for conatumumab versus 10% of subjects for placebo. Table 12 summarizes the most frequently reported grade ≥ 3 treatment-emergent adverse events from both the primary analysis and the final analysis.

Table 12. Most Frequently Reported (≥ 5%) Grade 3, 4, and 5 Treatment-emergent Adverse Events (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Preferred Term	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 50)	Placebo + Cotherapy (N = 51)	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 51)
Subjects reporting at least 1 grade 3, 4, or 5 adverse event	36 (72)	24 (47)	39 (76)	29 (57)
Neutropenia	15 (30)	9 (18)	15 (29)	11 (22)
Diarrhoea	9 (18)	5 (10)	10 (20)	6 (12)
Fatigue	4 (8)	2 (4)	5 (10)	3 (6)
Abdominal pain	4 (8)	2 (4)	4 (8)	2 (4)
Vomiting	4 (8)	3 (6)	4 (8)	3 (6)
Asthenia	3 (6)	3 (6)	4 (8)	3 (6)
Decreased appetite	4 (8)	0 (0)	4 (8)	0 (0)
Dehydration	3 (6)	1 (2)	3 (6)	1 (2)
Weight decreased	3 (6)	0 (0)	3 (6)	0 (0)
Anaemia	2 (4)	2 (4)	2 (4)	3 (6)
Intestinal obstruction	2 (4)	4 (8)	2 (4)	5 (10)
Mucosal inflammation	1 (2)	2 (4)	1 (2)	3 (6)
Hyperglycaemia	0 (0)	2 (4)	0 (0)	3 (6)

Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using CTCAE.
Source: Table 14-6.13 (Primary analysis); Table 14-6.9 (Final analysis)

Serious Treatment-emergent Adverse Events

As of the final analysis, the overall incidence of treatment-emergent serious adverse events was higher in the conatumumab treatment arm (43%) than the placebo treatment arm (31%) (Table 14-6.14, FA). The frequencies for 2 serious adverse events were > 5% higher in the conatumumab arm than the placebo arm: pyrexia (6% and 0%, respectively) and febrile neutropenia (6%, 0%). Table 13 summarizes the serious adverse events reported in ≥ 5% of subjects in either treatment arm from the primary analysis and the final analysis.

Detailed narratives for subjects with serious adverse events reported throughout the study are provided in Appendix 5.

Table 13. Most Frequently Reported (≥ 5%) Treatment-emergent Serious Adverse Events (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Preferred Term	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 50)	Placebo + Cotherapy (N = 51)	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 51)
Subjects reporting at least 1 serious adverse event	20 (40)	12 (24)	22 (43)	16 (31)
Diarrhoea	5 (10)	3 (6)	5 (10)	3 (6)
Vomiting	3 (6)	2 (4)	3 (6)	2 (4)
Pyrexia	4 (8)	0 (0)	3 (6)	0 (0)
Febrile neutropenia	1 (2)	0 (0)	3 (6)	0 (0)
Dehydration	3 (6)	0 (0)	2 (4)	0 (0)
Intestinal obstruction	2 (4)	2 (4)	2 (4)	3 (6)

Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using CTCAE.
Source: Table 14-6.14 (Primary analysis); Table 14-6.14 (Final analysis)

Deaths

At the final analysis, a total of 41 (80%) subjects in the conatumumab treatment arm and 36 (71%) subjects in the placebo treatment arm had died in the study (Listing 14-6.2, FA), which represents an additional 24 deaths and 18 deaths, respectively, since the primary analysis (Table 14-6.45, PA). For most of these subjects, overall, the primary cause of death was disease progression.

As of the final analysis, the deaths for 3 subjects in the conatumumab treatment arm resulted from treatment-emergent adverse events of colorectal cancer, death, and neoplasm malignant (this event reported after the primary analysis). The event of "death" was reported for Subject [redacted], a [redacted] with a past history of massive liver metastases and anemia who was found dead at home, cause unknown. There was no prior complaint of symptoms, and no other information was available. The death occurred 5 days after the last administration of conatumumab (Listing 14-6.1, FA; Listing 14-6.2, FA; Listing 14-2.2, PA; Listing 14-4.2, PA). The death was considered to be related to investigational product and chemotherapy. The other 2 fatal events (colorectal cancer and neoplasm malignant) were not considered to be related to any protocol-specified treatment. There were no fatal treatment-emergent adverse events in the placebo treatment arm.

Detailed narratives for subjects with fatal adverse events reported throughout the study are provided in Appendix 5.

Treatment-emergent Adverse Events Leading to Study Withdrawal or Discontinuation of Therapy

At the time of the final analysis, the incidence of treatment-emergent adverse events in the conatumumab and placebo treatment arms leading to withdrawal from the study (2% [1 subject] in each treatment arm) was unchanged from the primary analysis (Table 14-6.15, PA; Table 14-6.1, FA). For conatumumab, the event was grade 5 neoplasm malignant (serious); for

placebo, the event was grade 3 metastases to central nervous system (serious) (Listing 14-6.3, FA) (both of these events were due to disease progression).

The summary of treatment-emergent adverse events leading to discontinuation of investigational product at the final analysis increased from the primary analysis: 11 (22%) subjects in the conatumumab treatment arm (3 additional subjects since the primary analysis) and 5 (10%) subjects in the placebo treatment arm (1 additional subject since the primary analysis) (Table 14-6.45, FA). Adverse events leading to discontinuation of investigational product in the conatumumab arm included febrile neutropenia, thrombocytopenia, abdominal pain, diarrhea, vomiting, asthenia, death, infusion-related reaction, blood alkaline phosphatase increased, weight decreased, dehydration (2 subjects), hypoalbuminemia, hypocalcemia, neoplasm malignant, and loss of consciousness (the 3 additional events since the primary analysis were febrile neutropenia, hypocalcemia, and neoplasm malignant [Listing 14-6.3, FA]); in the placebo arm, these events included pancytopenia, abdominal pain, diarrhea, metastases to central nervous system, and cardiac failure congestive (the additional event since the primary analysis [Listing 14-6.3, FA]).

As of the final analysis, treatment-emergent adverse events leading to discontinuation of all protocol-specified therapy occurred in 9 (18%) subjects in the conatumumab treatment arm and 3 (6%) subjects in the placebo treatment arm; these results represent an increase from the primary analysis of 3 subjects in the conatumumab treatment arm (Table 14-6.46, FA; Listing 14-6.8, PA; Listing 14-6.3, FA). The adverse events leading to discontinuation of all protocol-specified therapy in the conatumumab treatment arm were hypocalcemia, hypoalbuminemia, loss of consciousness, infusion-related reaction, blood alkaline phosphatase increased, thrombocytopenia, febrile neutropenia, death, and neoplasm malignant (the 3 additional events since the primary analysis were febrile neutropenia, hypocalcemia, and neoplasm malignant [Listing 14-6.3, FA]); the events leading to discontinuation of all protocol-specified therapy in the placebo treatment arm were diarrhea, pancytopenia, and congestive cardiac failure (the additional event since the primary analysis [Listing 14-6.3, FA]).

Adverse Events of Interest

Adverse events of interest for conatumumab include increased serum amylase and lipase, hypomagnesemia, hyponatremia, infusion reaction, and venous thromboembolic events. Search strategies using broad and narrow search terms were implemented at both the primary and final analyses; for this clinical study report, the focus is on the output using the narrow search strategy for each event of interest.

By the time of the final analysis, the overall frequency of adverse events of interest was similar between the conatumumab (18%) and placebo (16%) treatment arms (Table 14-6.49, FA). Hypomagnesemia and infusion reaction were reported most often in the conatumumab arm at the final analysis, and they occurred at higher frequencies in the conatumumab arm than the placebo arm (hypomagnesemia: 12% and 2%, respectively; infusion reaction: 12%, 6%). Increased amylase and lipase, hyponatremia, and venous thromboembolic events occurred at generally similar frequencies in the 2 treatment arms. Adverse events of interest that were grade ≥ 3 occurred in ≤ 2 subjects in each event of interest.

An overview of the adverse events of interest from the primary analysis and the final analysis is provided in Table 14.

Table 14. Incidence of Treatment-emergent Adverse Events of Interest Narrow Search Terms (Safety Analysis Set)

Event of Interest Category	Primary Analysis				Final Analysis			
	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 50) n (%)		Placebo + Cotherapy (N = 51) n (%)		AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51) n (%)		Placebo + Cotherapy (N = 51) n (%)	
Subjects reporting any adverse event of interest	14 (28)		10 (20)		9 (18)		8 (16)	
	Total	Grade ≥ 3	Total	Grade ≥ 3	Total	Grade ≥ 3	Total	Grade ≥ 3
Increased serum amylase and lipase	3 (6)	1 (2)	3 (6)	1 (2)	3 (6)	2 (4)	4 (8)	1 (2)
Hypomagnesemia	6 (12)	1 (2)	2 (4)	0 (0)	6 (12)	1 (2)	1 (2)	0 (0)
Hyponatremia	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
Infusion reaction	5 (10)	2 (4)	3 (6)	0 (0)	6 (12)	2 (4)	3 (6)	0 (0)
Treatment-related infusion reaction	3 (6)	1 (2)	1 (2)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)
Venous thromboembolic events	3 (6)	1 (2)	1 (2)	1 (2)	3 (6)	1 (2)	3 (6)	2 (4)

Note: The cotherapy is FOLFIRI.
Note: Adverse events were coded using MedDRA version 13.1 for the primary analysis and version 15.0 for the final analysis and graded using CTCAE.
Source: Table 14-6.62 (Primary analysis); Table 14-6.49 (Final analysis)

Clinical Laboratory Evaluations

The incidence of treatment-emergent grade ≥ 3 chemistry and hematology laboratory values as of the final analysis was similar between the conatumumab and placebo treatment arms for most of the analytes; one analyte had a > 5% higher incidence of grade ≥ 3 treatment-emergent values in the conatumumab arm versus placebo (lymphocytes: 14% and 8%, respectively) (Table 14-7.2, FA).

Table 15 presents the frequencies of grade ≥ 3 chemistry and hematology values for the primary analysis compared with the final analysis. The results were consistent between the 2 analyses.

Change from baseline in chemistry analytes for the final analysis are summarized in Table 14-7.6, FA through Table 14-7.16, FA and Table 14-7.18, FA through Table 14-7.24, FA. Change from baseline in hematology analytes for the final analysis are summarized in Table 14-7.17, FA and Table 14-7.25, FA through Table 14-7.37, FA.

Table 15. Incidence of Treatment-emergent NCI CTCAE Grade ≥ 3 (Safety Analysis Set)

	Primary Analysis		Final Analysis	
Category Analyte	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 50)	Placebo + Cotherapy (N = 51)	AMG 655 10 mg/kg (Q2W) + Cotherapy (N = 51)	Placebo + Cotherapy (N = 51)
Chemistry				
ALT	2 (4)	0 (0)	2 (4)	0 (0)
Albumin	1 (2)	0 (0)	1 (2)	0 (0)
Alkaline phosphatase	1 (2)	2 (4)	2 (4)	3 (6)
Amylase	2 (4)	0 (0)	2 (4)	0 (0)
AST	2 (4)	0 (0)	2 (4)	1 (2)
Bicarbonate	0 (0)	0 (0)	0 (0)	0 (0)
Calcium	1 (2)	0 (0)	1 (2)	0 (0)
Glucose	0 (0)	3 (6)	0 (0)	3 (6)
Lipase	4 (8)	2 (4)	4 (8)	2 (4)
Magnesium	1 (2)	0 (0)	1 (2)	0 (0)
Phosphorus	2 (4)	0 (0)	2 (4)	1 (2)
Potassium	4 (8)	2 (4)	6 (12)	4 (8)
Sodium	0 (0)	0 (0)	0 (0)	1 (2)
Total bilirubin	2 (4)	1 (2)	3 (6)	1 (2)
Hematology				
Absolute neutrophil count	14 (28)	10 (20)	14 (27)	12 (24)
Hemoglobin	2 (4)	2 (4)	2 (4)	3 (6)
Lymphocytes	8 (16)	3 (6)	7 (14)	4 (8)
Platelets	1 (2)	1 (2)	1 (2)	1 (2)
White blood cells	5 (10)	4 (8)	6 (12)	4 (8)

Note: The cotherapy is FOLFIRI.
Note: Based on NCI-CTCAE Version 3.0.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI = National Cancer Institute; CTCAE = Common Terminology Criteria for Adverse Events.
Source: Table 14-7.79 and Table 14-7.80 (Primary analysis); Table 14-7.2 (Final analysis)

At the final analysis, no subjects in either the conatumumab or placebo treatment arms exhibited liver analyte abnormalities that met the criteria for Hy's Law on the same day (Table 14-7.40, FA). One subject in the conatumumab treatment arm, Subject [redacted], with a prior medical history of extensive metastatic disease including liver, lymph node, and lung parenchymal metastases, exhibited abnormalities that met these criteria on different days (Listing 14-7.3, FA; Listing 14.4.2, PA). Values for total bilirubin and alkaline phosphatase each met the individual criteria at multiple time points during the study, and AST met the individual criteria at one time point. The highest total bilirubin for this subject occurred on study day 727 (82.1 µmol/L, grade 3), and the highest AST occurred on day 727 (99 U/L, grade 2). Alkaline phosphatase was ≤ 2 × ULN at most time points. Multiple adverse events of blood bilirubin increased were reported during the study, none of which were considered to be related to investigational product (Listing 14-6.4, FA). This subject was treated for 46 cycles and was discontinued due to a serious adverse event of grade 4 febrile neutropenia on day 736 (Listing 14-6.4, FA).

Other Evaluations:

Antibody Results

Antibody results below are presented separately for ganitumab and conatumab.

Ganitumab

Final analysis results of the incidence of subjects testing positive for anti-ganitumab antibodies were similar to those described in the primary analysis: 4 (8%) subjects in the ganitumab treatment arm, 5 (10%) subjects in the conatumumab treatment arm, and 7 (15%) subjects in the placebo treatment arm tested positive for pre-existing anti-ganitumab antibodies (Table 14-8.2, FA). In addition, 1 subject in the ganitumab treatment arm and 2 subjects in the placebo treatment arm who were negative at baseline tested positive for anti-ganitumab antibodies (non-neutralizing) during the treatment period (Listing 14-7.5, FA): Subject [redacted] (ganitumab) tested positive for the anti-ganitumab antibodies on day 51 (safety follow-up visit). At this time, adverse events included hypotension, anemia, and hypoalbuminemia. Subject [redacted] (placebo) tested positive on day 113 (cycle 9, day 1) and day 154 (safety follow-up visit). On day 113, adverse events included mucositis and nausea. On day 48, the subject experienced fatigue. Subject [redacted] (placebo) tested positive on day 134 (cycle 9, day 1). On day 124, the subject experienced neutropenia; no further events were reported. Overall, none of these adverse events were likely to have resulted from the presence of anti-ganitumab antibodies. Anti-ganitumab antibodies detected at baseline or during treatment with placebo, despite never having received a dose of ganitumab, are likely to represent cross-reactive antibodies that are present as a consequence of molecular mimicry.

Conatumumab

Final analysis results of the incidence of subjects testing positive for anti-conatumumab antibodies were similar to those described in the primary analysis: 2 (4%) subjects in the conatumumab treatment arm and 2 (4%) subjects in the ganitumab treatment arm tested positive for pre-existing anti-conatumumab antibodies (Table 14-8.1, FA). In addition, 1 subject in the conatumumab treatment arm (Subject [redacted]) who tested negative at baseline tested positive for anti-conatumumab antibodies and neutralizing antibodies postbaseline on day 93 (cycle 5, day 1) (Listing 14-7.5, FA). As described in the primary analysis clinical study report, a medical review of the adverse events for this subject indicated that the adverse events experienced by this subject were unlikely to have been a result of the presence of anti-conatumumab antibodies (section 11.3.10 of the primary analysis clinical study report).

Pharmacokinetic Results

Pharmacokinetics results for ganitumab and conatumumab are presented separately below. Pharmacokinetics results for irinotecan, its metabolite SN-38, and 5-FU are presented for ganitumab, conatumumab, and placebo groups. Individual concentration data (ganitumab, conatumumab, irinotecan, SN-38, and 5-FU) are presented in Appendix 7.

Ganitumab

Ganitumab end-of-infusion (C_{max}) and pre-infusion (C_{min}) values through cycle 17 are listed in Table 16. With the Q2W regimen, the mean end-of-infusion (C_{max}) concentrations observed in cycle 1 and cycle 3 were 186 and 227 µg/mL, respectively. The accumulation of ganitumab, as assessed by C_{max}, between cycles 1 and 3, was approximately 1.2-fold in this study. The mean pre-infusion concentration (C_{min}) for cycles 3, 5, 9, 13, and 17 ranged from 29.9 to 54.8 µg/mL. Additional details are provided in the pharmacokinetics clinical study report contribution (Appendix 7).

Table 16. Descriptive Statistics of Ganitumab End-of-infusion and Pre-infusion Concentrations After Intravenous Administration of 12 mg/kg Ganitumab Every 2 Weeks in Combination With FOLFIRI

	Cycle 1		Cycle 3		Cycle 5	Cycle 9	Cycle 13	Cycle 17
	Pre	EOI	Pre	EOI	Pre	Pre	Pre	Pre
N	48	40	32	34	27	18	11	10
Mean	2.20	186	29.9	227	34.9	41.0	48.4	54.8
SD	14.7	49.0	13.8	107	18.2	21.1	23.1	24.4
Range	(0.00 - 102)	(101 - 298)	(5.43 - 64.1)	(28.7 - 698)	(6.56 - 79.7)	(3.26 - 91.7)	(12.2 - 86.8)	(23.0 - 96.3)

Pre = pre-infusion; EOI = end of infusion; SD = standard deviation.
Note: All concentrations are reported in µg/mL.
Source: PKS/Study20060579 final analysis mapping/Base Scenario/Desc Stats w/excl/AMG479/655 (Version 3)

Conatumumab

Conatumumab end-of-infusion (C_{max}) and predose (C_{min}) values through cycle 17 are listed in Table 17. The mean end-of-infusion (C_{max}) concentrations observed in cycle 1 and cycle 3 were 178 and 216 µg/mL, respectively. The accumulation of conatumumab between cycle 1 and steady state (cycle 5) cannot be assessed due to the preset sampling scheme. The accumulation of C_{max} between cycles 1 and 3 was approximately 1.2-fold in this study. The mean pre-infusion (C_{min}) concentration observed in cycles 3, 5, 9, 13, and 17 ranged from 77.0 to 136 µg/mL. Additional details are provided in the pharmacokinetics clinical study report contribution (Appendix 7).

Table 17. Descriptive Statistics of Conatumumab End-of-infusion and Pre-infusion Concentrations After Intravenous Administration of 10 mg/kg Conatumumab Every 2 Weeks in Combination With FOLFIRI

	Cycle 1		Cycle 3		Cycle 5	Cycle 9	Cycle 13	Cycle 17
	Pre	EOI	Pre	EOI	Pre	Pre	Pre	Pre
N	48	41	29	28	26	14	13	7
Mean	2.94	178	77.0	216	94.0	120	130	136
SD	20.4	63.3	28.4	62.1	29.5	36.6	38.3	51.6
Range	(0.00 - 141)	(54.3 - 355)	(18.4 - 144)	(112 - 345)	(49.8 - 145)	(34.0 - 193)	(67.4 - 182)	(87.2 - 231)

Concentrations below the limit of quantification for conatumumab (0.0299 µg/mL) were set to zero.
Pre = pre-infusion; EOI = end of infusion; SD = standard deviation.
Note: All concentrations are reported in µg/mL.
Source: PKS/Study20060579 final analysis mapping/Base Scenario/Desc Stats w/excl/AMG479/655 (Version 3)

Irinotecan and 5-FU

Following IV infusion of 180 mg/m^2 irinotecan, mean (SD) irinotecan C_{max} values were 1950 (626), 1910 (388), and 1860 (522) ng/mL in ganitumab, conatumumab, and placebo treatment groups, respectively. Mean (SD) irinotecan AUC_{inf} values were 13,500 (3390), 17,400 (3610), and 14,100 (3120) ng•hr/mL, respectively. The metabolite of irinotecan (ie, SN-38) had mean (SD) C_{max} values of 23.6 (9.51), 21.0 (13.0), and 27.1 (9.13) ng/mL and mean (SD) AUC_{inf} values of 374 (126), 340 (121), and 432 (149) ng•hr/mL in the ganitumab, conatumumab, and placebo groups, respectively. [redacted]

The median 5-FU concentration values at 3 hours were 343, 282, and 374 ng/mL in cycle 1 and 320, 287, and 307 ng/mL in cycle 3 for the ganitumab, conatumumab, and placebo treatment groups, respectively. The median concentrations at 24 hours were 449, 400, and 466 ng/mL in cycle 1 and 361, 441, and 389 ng/mL in cycle 3 for the 3 treatment groups, respectively. [redacted] Additional details are provided in the pharmacokinetics clinical study report contribution (Appendix 7).

Conclusions:

Based on the final study results, the addition of ganitumab or conatumumab to FOLFIRI as second-line treatment in subjects with mutant *KRAS* mCRC did not appear to improve PFS or OS over FOLFIRI alone. Based on the final analysis safety data, no new safety signals were observed with the combination of ganitumab and FOLFIRI or conatumumab and FOLFIRI. [redacted] The overall conclusions from the final analyses in this study are generally consistent with those drawn in the primary analysis clinical study report.

Reference List:

Cohn AL, Tabernero J, Maurel J, et al. Conatumumab (CON) + FOLFIRI (F) or Ganitumab (GAN) + F for Second-line Treatment of Mutant (MT) KRAS Metastatic Colorectal Cancer (mCRC) [poster]. ASCO Gastrointestinal Cancers Symposium, 2012. Abstract 534.