Title: A Phase 2 Open Label Extension Study of Conatumumab and AMG 479

AMG 655 (Conatumumab) and AMG 479

Amgen Protocol Number 20101116
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Amendment 4:	20 November 2013
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Confidentiality Notice

NCT Number: NCT01327612
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Investigator's Agreement

I have read the attached protocol entitled A Phase 2 Open Label Extension Study of Conatumumab and AMG 479, dated **11 April 2017**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 2 Open Label Extension Study of Conatumumab and AMG 479

Study Phase: 2

Indication: Subjects who have completed a separate Amgen-sponsored conatumumab or AMG 479 study and will continue treatment according to the parent study.

Primary Objective: To provide ongoing treatment with**:**

- conatumumab therapy, with or without co-therapy (chemotherapy with and without bevacizumab, or AMG 479) for subjects who are eligible, according to the parent study, to receive their next dose of conatumumab, or
- AMG 479 therapy alone, for subjects who are eligible, according to the parent study, to receive their next dose of AMG 479.

Secondary Objective(s): To evaluate the safety profile, including adverse events and serious adverse events, of:

- conatumumab, with or without co-therapy, or
- AMG 479 alone.

Hypotheses: The purpose of this study is to provide a mechanism for subjects to continue to receive treatment with conatumumab and/or AMG 479.

Study Design

This is a Phase 2 multi-center, open-label study that permits subjects who have completed a separate Amgen-sponsored conatumumab or AMG 479 study to continue treatment with conatumumab, with or without co-therapy (chemotherapy with and without bevacizumab, or AMG 479), or with AMG 479 therapy alone. Subjects who have not progressed on a separate Amgen protocol are eligible to participate in this trial.

In this extension study, conatumumab and AMG 479 study drugs will be administered at the same dose level and schedule that the subject received at the conclusion of the parent conatumumab, or AMG 479 study, accommodating any subjects who were maintained on a reduced dose level or different schedule of administration in their parent study.

Subjects will be evaluated before every cycle of conatumumab or AMG 479 therapy at the study clinic. These study visits will include a standard of care clinical assessment which includes collection of vital signs, adverse events, concomitant medications, and laboratory samples and results. Radiological assessments to evaluate disease extent (with change compared to nadir from the parent protocol) should be performed at regular intervals, at a minimum once every 6 (± 1) months or more frequently if clinically indicated (starting from their last scan on the parent protocol), per standard of care (SOC) at each facility.

Reasons for study discontinuation will include progressive disease, intolerance to investigational product(s), and/or need for additional systemic anticancer treatment. When a subject discontinues the study for any reason, a safety follow-up visit will be completed at least 30 (+ 3) days after the last dose of protocol-specified therapy.

Primary and Secondary Endpoints

- Adverse events
- Serious adverse events
- Vital signs
- Clinical laboratory tests
- Tumor response
- Disease progressions and deaths

Sample Size: The sample size is dependent upon the number of subjects that transition into this study from separate Amgen conatumumab or AMG 479 studies. The sample size is estimated to be approximately 15 subjects.

Summary of Subject Eligibility Criteria

Inclusion Criteria

To be enrolled in this study, subjects must be currently enrolled in a prior Amgen-sponsored conatumumab or AMG 479 study, and are eligible according to the parent study to receive their next dose of conatumumab (with or without co-therapy) or AMG 479 alone.

Subjects must have their eligibility assessed for this study and be enrolled within 30 days of their last treatment on the parent protocol.

Exclusion Criteria

Discontinued from a conatumumab or AMG 479 study due to an adverse event, including intolerance to conatumumab or AMG 479, respectively.

Subjects determined to have disease progression during their participation in the parent Amgen study.

Amgen Investigational Product Dosage and Administration

The starting dose and frequency of conatumumab will be determined based on the dose and frequency administered during the parent study.

Conatumumab will be administered by IV infusion. The dose of conatumumab will be calculated based on the subject's actual body weight during the study day 1 assessment and the dose must be recalculated if actual body weight changes by ± 10%. Investigators may recalculate the doses more frequently based on institutional guidelines.

Subjects previously enrolled in Study 20070411 will receive conatumumab and/or AMG 479 per parent protocol. AMG 479 18 mg/kg will be administered IV Q3W, unless discontinued during treatment on parent protocol. Subjects previously enrolled in Study 20050118 will receive AMG 479 monotherapy at a dosed of 20 mg/kg IV Q3W or Q4W per parent protocol. There will be no individual AMG 479 dose reductions, except as outlined below in Table 5, Thrombocytopenia without Bleeding.

The dose (infusion volume) of AMG 479 will be calculated based on the subject's actual body weight during the study day 1 assessment. The dose will not need to be recalculated unless the actual body weight changes by ± 10%. Investigators may recalculate the dose of AMG 479 more frequently according to institutional guidelines.

AMG 479 will be administered through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding filter with a 0.2- or 0.22- micron pore size in-line filter infusion set-up.

Non Amgen Non-investigational Product Dosage and Administration

Subjects previously enrolled in Study 20060464 subjects will be treated with mFOLFOX6 and bevacizumab on each of the 14 day (+ 3 days) treatment cycles before infusion of conatumumab (2 or 10 mg/kg Q2W, based on their dose from study 20060464).

Modified FOLFOX6 regimen is a combination therapy of oxaliplatin (85 mg/m^2) administered as a 2-hour infusion on day 1; leucovorin (400 mg/m^2 racemate or 200 mg/m^2 levo-leucovorin) administered as a 2-hour infusion on day 1; followed by a loading dose of 5-FU (400 mg/m^2) IV bolus administered on day 1, then 5-FU (2,400 mg/m^2) via ambulatory pump administered for a period of 46-48 hours every 14 days (+ 3 days).

Administration of mFOLFOX6 chemotherapy will commence on day 1 of each treatment cycle and end with a continuous IV infusion of 5-FU. For the purpose of this protocol, the administration of continuous IV infusion of 5 FU will commence after conatumumab infusions.

A new cycle of mFOLFOX6 treatment will be repeated every 2 weeks (+ 3 days).

Bevacizumab will be administered at a dose of 5 mg/kg by intravenous infusion on day 1 of each 14 day cycle (+ 3 days). Institutional standards for bevacizumab infusion times may be used.

Control Group: N/A

Procedures

Eligibility Assessment for Continued Treatment

- Review of inclusion and exclusion criteria
- Medical history and concomitant medications
- Vital signs, physical exam and height
- Pregnancy test as applicable

Treatment and Follow-up Procedures

- Recording of adverse events and concomitant medications
- Vital signs and weight
- Laboratory samples: including hematology, chemistry, amylase, lipase, coagulation, urinalysis, glucose as appropriate
- Samples for anti-conatumumab antibodies, samples for anti-AMG 479 antibodies as appropriate
- Radiological assessments to evaluate disease extent (with change compared to nadir from the parent protocol) should be performed at regular intervals, at a minimum once every 6 (± 1) months or more frequently if clinically indicated (starting from their last scan on the parent protocol), per standard of care (SOC) at each facility

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Appendix A.

Statistical Considerations:

The studies preceding this open label extension are sufficiently different to preclude pooling of data over the studies. Since the number of subjects enrolled per parent study will be low most of the data will be shown in listings. A limited number of summary tables will be produced when the number of subjects makes this sensible.

The final analysis of this study will be performed at the end of the study ie, when all the subjects have completed or had the opportunity to complete the Day 60 Follow-up visit. The data may be summarized and listed before the final analysis to support Regulatory filings.

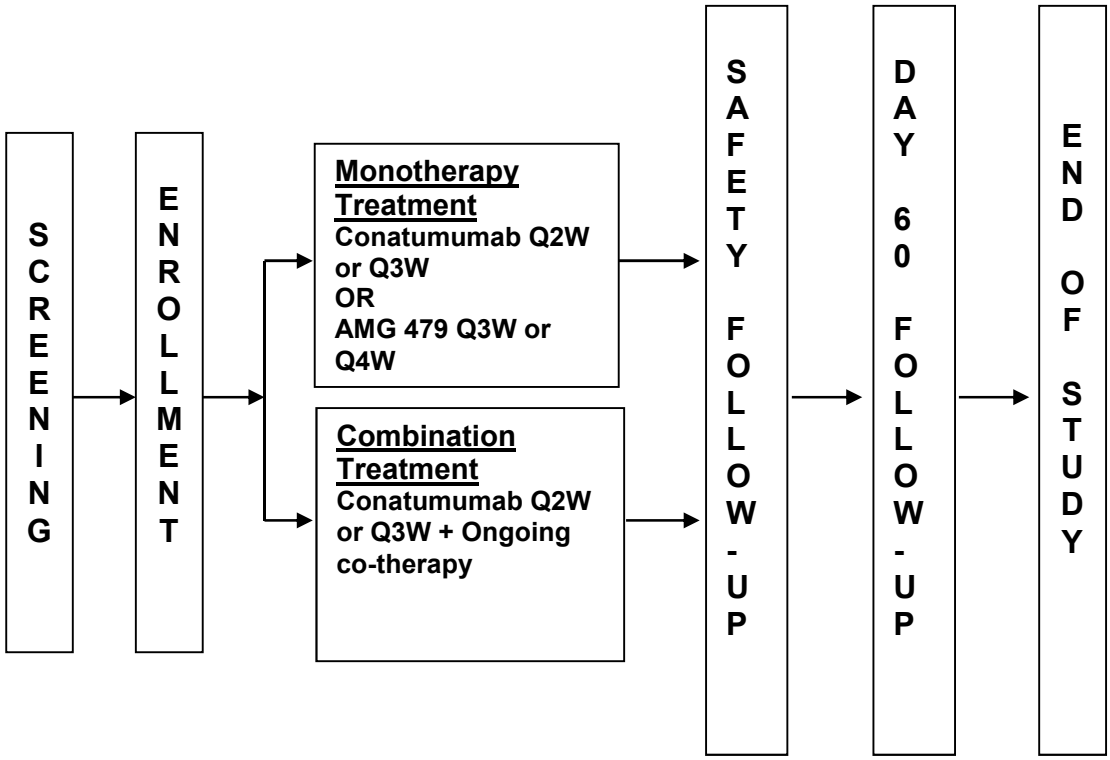
Subject disposition (number screened, enrolled into the study, receive conatumumab and/or AMG 479, withdraw from the study) will be summarized.

Demographics (age, sex, race) and tumor type will be listed.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor/Licensee: Amgen Inc.

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
5-FU	5-fluorouracil
ADL	activities of daily living
Adverse Event	Any event that occurs after the start of study treatment. These will be collected for all enrolled subjects.
ALT (SGPT)	alanine aminotransferase (serum glutamic-pyruvic transaminase)
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase
Baseline Value	The "baseline value" is the value measured on study Day 1 before first administration of study specified treatment. For variables/assessments not scheduled to be performed on study Day 1 or that are missing at baseline, the baseline value is the value from the screening period measured closest to study Day 1.
BUN	blood urea nitrogen
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Co-therapy	Defined as either chemotherapy (including bevacizumab) or AMG 479. This definition applies to subjects who are eligible to receive conatumumab in combination with co-therapy according to the parent study.
Day 60 Follow-up Visit	The study visit at 60 days (± 14 days) after last dose of protocol-specified therapy.
Disease Progression	Refers to radiographic progression or clinical progression
DR5	Death receptor 5
eCRF	electronic case report form
End of Study	When all the subjects have completed or had the opportunity to complete the Day 60 Follow-up visit
GCP	Good Clinical Practice
G-CSF	granulocyte-colony-stimulating factor
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF-1R	type I insulin-like growth factor receptor
IgG1	immunoglobulin G, type 1
Investigational product	Refers to either conatumumab or AMG 479
IRB	institutional review board
INR	international normalization ratio

Abbreviation or Term	Definition/Explanation
IP	investigational product
IV	intravenous
LLN	lower limit of normal
LV	leucovorin
On-Study Death	Any death that occurs after receiving protocol specified therapy through 30 days after the last dose of IP. Any on-study death will be reported as a serious adverse event.
Parent Study	refers to protocol under which subjects received their initial treatment with conatumumab
PK	pharmacokinetics
PLT	platelets
PTT	prothrombin time
Q2W	every two weeks
Q3C	every three cycles
Q8C	every eight cycles
SAE	serious adverse event
SAER	Serious Adverse Event Report
Safety Follow-up (30 Day Safety Follow-up Visit)	The study visit at 30 days (+ 3 days) after last dose of protocol-specified therapy.
Screen Failure	A subject who signs an informed consent but fails to enroll in the study.
SOC	Standard of care
Study Day 1	The day that the first dose of study specified treatment is administered.
Study End	When all the subjects have completed or had the opportunity to complete the Day 60 Follow-up visit
Study end for each subject	The date the subject withdraws consent from the study, completes or has the opportunity to complete the Day 60 follow-up visit or dies.
Study Start	The study will start when the first subject has been enrolled.
Study Week 1	The 7-day period beginning with study Day 1 through study Day 7.
TNF	tumor necrosis factor
TRAIL	tumor necrosis factor (TNF)-related apoptosis-inducing ligand
ULN	upper limit of normal
WBC	white blood cell

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1. OBJECTIVES

1.1 Primary

To provide ongoing treatment with:

- conatumumab therapy, with or without co-therapy (chemotherapy with and without bevacizumab, or AMG 479), for subjects who are eligible, according to the parent study, to receive their next dose of conatumumab, or
- AMG 479 therapy alone for subjects who are eligible, according to the parent study, to receive their next dose of AMG 479.

1.2 Secondary

To evaluate the safety profile, including adverse events and serious adverse events, of:

- conatumumab, with or without co-therapy, or
- AMG 479 alone.

2. BACKGROUND AND RATIONALE

2.1 Disease

This protocol will include subjects previously enrolled in Amgen-sponsored conatumumab and AMG 479 studies with different solid tumors, including, but not limited to, colorectal cancer (CRC), non small cell lung cancer (NSCLC), soft tissue sarcoma (STS), non-Hodgkin's lymphoma (NHL), pancreatic cancer, and ovarian cancer.

2.2 Amgen Investigational Product Background

2.2.1 Conatumumab Background

2.2.1.1 Death Receptor 5 and Cancer

Apoptosis or programmed cell death is an evolutionarily conserved process for removing unwanted cells from the body. Dysregulation of this process contributes to many diseases including cancer. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor 2 (TR-2, death-receptor 5 [DR5]) is a member of the tumor necrosis factor super-family of receptors. TRAIL is the natural ligand for DR5; TRAIL binding to DR5 initiates an intracellular caspase cascade and induces apoptosis in many human transformed cell lines but not most normal cells (Kelly and Ashkenazi, 2004).

TRAIL receptor agonists have been demonstrated to induce apoptosis in a variety of cancer cell lines with little toxicity to normal cells. There is also evidence that they may act cooperatively with existing cancer therapies, including targeted agents. These findings suggest that stimulating DR5 could be useful for cancer therapy in combination with a range of existing anti-tumor therapies on a wide variety of tumor types.

2.2.1.2 Conatumumab Clinical Experience

As of 18 June 2010, approximately 973 subjects have been enrolled in 10 ongoing clinical trials of conatumumab; 80 have received monotherapy and 749 have received conatumumab (or conatumumab-placebo) in combination with chemotherapy and/or other biologic agents.

A brief description and status of each study in the conatumumab clinical development program are provided in Table 1. For details regarding the safety and efficacy of conatumumab indications, please refer to the latest edition of conatumumab IB.

Table 1. Summary of Clinical Studies

Study Number	Study Title	Study Status	Dose[a]	Enrollment[b]
Conatumumab Administered as Monotherapy				
20050171	A Phase 1, Open-Label, Dose Escalation Study Evaluating the Safety, Tolerability and Pharmacokinetics of Conatumumab in Subjects with Advanced Tumors	Ongoing; primary analysis complete	Part 1: 0.3, 1, 3, 10, or 20 mg/kg IV Q2W Part 2: 20 mg/kg IV Q2W	Part 1: 22 Part 2: 15
20060246	A Phase 1, Open-Label, Dose Escalation Study Evaluating the Safety, Tolerability and Pharmacokinetics of Conatumumab in Japanese Subjects with Advanced Tumors	Ongoing; primary analysis complete	3, 10, or 20 mg/kg IV Q2W	18
Conatumumab Administered in Combination with Chemotherapy				
20060323	A Phase 1b/2 Study to Evaluate the Safety and Efficacy of Conatumumab or AMG 479 in Combination with Gemcitabine as First-Line Therapy for Metastatic Pancreatic Cancer	Ongoing; preliminary data	Part 1: 3 or 10 mg/kg IV Q2W in combo with gemcitabine Part 2: conatumumab 10 mg/kg IV Q2W, AMG 479 12 mg/kg IV Q2W, or conatumumab-placebo in combination with gemcitabine	Part 1: 13 Part 2: 125

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[a] Refers to conatumumab dose unless otherwise noted.
[b] As of the data cutoff date of 09 July 2009

Table 1. Summary of Clinical Studies

Study Number	Study Title	Study Status	Dose[a]	Enrollment[b]
Conatumumab Administered in Combination with Chemotherapy (continued)				
20060295	A Phase 1b/2 Study of Conatumumab in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Non-Small Cell Lung Cancer	Ongoing; primary analysis complete	Part 1: 5 or 15 mg/kg IV Q3W in combination with paclitaxel/ carboplatin Part 2: conatumumab (15 mg/kg), conatumumab (3 mg/kg), or conatumumab-placebo IV Q3W in combination with paclitaxel/carboplatin	Part 1: 12 Part 2: 172
20060464	A Phase 1b/2 Study of Conatumumab in Combination with Modified FOLFOX6 and Bevacizumab for the First-Line Treatment of Subjects with Metastatic Colorectal Cancer	Ongoing; preliminary data	Part 1: 3 or 10 mg/kg IV Q2W in combination with mFOLFOX6/ bevacizumab Part 2: conatumumab (10 mg/kg), conatumumab (2 mg/kg), or conatumumab placebo IV Q2W in combination with mFOLFOX6 and bevacizumab	Part 1: 12 Part 2: 186
20060324	A Phase 1b/2 Study of Conatumumab in Combination With Doxorubicin for the First-Line Treatment of Locally Advanced or Metastatic, Unresectable Soft Tissue Sarcoma	Ongoing; preliminary data	Part 1: 15 mg/kg IV Q3W in combination with doxorubicin Part 2: conatumumab (15 mg/kg), or placebo IV Q3W in combination with doxorubicin	Part 1: 6 Part 2: 128
20060340	A Phase 1b Study to Evaluate the Safety and Tolerability of Conatumumab in Combination with Bortezomib or Vorinostat in Subjects with Relapsed or Refractory Lymphoma	Ongoing; preliminary data	Part 1: 1.5, 5 or 15 mg/kg IV Q3W in combination with bortezomib or vorinostat Part 2: dose selected in part 1 in combination with bortezomib	Part 1: 27

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[a] Refers to conatumumab dose unless otherwise noted.
[b] As of the data cutoff date of 09 July 2009

Table 1. Summary of Clinical Studies

Study Number	Study Title	Study Status	Dose[a]	Enrollment[b]
Conatumumab Administered in Combination with Chemotherapy (continued)				
20060579	A Phase 2, double-blind Study to Evaluate the Safety and Efficacy of FOLFIRI in Combination With AMG 479 or Conatumumab Versus FOLFIRI for the Second-line Treatment of KRAS-mutant Metastatic Colorectal Carcinoma	Ongoing; preliminary data	10 mg/kg IV Q2W + AMG 479 placebo in combination with FOLFIRI, AMG 479 12 mg/kg + conatumumab placebo IV Q2W in combination with FOLFIRI, or conatumumab placebo + AMG 479 placebo in combination with FOLFIRI	8
Conatumumab Administered in Combination with Other Biologic Agents				
20060332	A Phase 1b/2 Study of Conatumumab in Combination with Panitumumab in Subjects with Metastatic Colorectal Cancer	Ongoing; primary analysis complete	Part 1: 10 mg/kg IV Q2W in combination with 6 mg/kg panitumumab IV Q2W Part 2: 10 mg/kg IV Q2W in combination with panitumumab	Part 1: 6 Part 2: 47
20070411	A Phase 1b/2, Dose Escalation Study of Conatumumab in Combination with AMG 479 in Subjects with Advanced, Refractory Solid Tumors	Ongoing; preliminary data	Part 1: 1, 3 or 15 mg/kg IV Q3W in combination with AMG 479 18 mg/kg Part 2: 15 mg/kg IV Q3W in combination with AMG 479	Part 1: 9

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[a] Refers to conatumumab dose unless otherwise noted.
[b] As of the data cutoff date of 09 July 2009

2.2.1.3 Conatumumab Pharmacokinetics

Based on noncompartmental analysis of all available PK data, conatumumab exhibited doselinear kinetics in the range from 0.3 to 20 mg/kg. The overall mean (median) half-life was 12 (10.7) days. Therefore, the human PK profile supports intravenous administration once every 2 to 3 weeks in subjects with cancer.

2.2.2 AMG 479 Background

Most human cancers express the type I insulin-like growth factor receptor (IGF-1R; Sachdev and Yeel, 2007; Macaulay, 1992; Werner and LeRoith, 1996). Tumor growth and survival is supported by IGF-1R signaling through stimulation of cell survival pathways that allow tumor cells to resist the apoptosis-inducing activity of

chemotherapeutics, radiation, and antihormone therapy. IGF-1R signaling inhibition has been shown to slow tumor growth in human xenografts. Moreover, IGF-1R inhibition has been shown to potentiate the anti-tumor effects of chemotherapy, radiation therapy, biologic and hormonal therapeutic agents in preclinical xenograft models. AMG 479, a fully human monoclonal antibody (IgG1) against human IGF-1R, was developed to inhibit survival and proliferative signals that are driven by IGF-1 and IGF-2. Treatment of human tumors with AMG 479 alone or in combination with other anti-cancer therapy should inhibit tumor growth and invasion.

2.2.3 AMG 479 Clinical Experience

Table 2. Clinical Studies With AMG 479 by Tumor Type

Protocol No.	Description	Status
Monotherapy Study in Mixed Solid Tumors		
20050118	A Phase 1, Open-Label, Dose Finding Study Evaluating the Safety and Pharmacokinetics of AMG 479 in Subjects with Advanced Solid Tumors	Ongoing
20060245	A Phase 1, Open-label, Dose Escalation Study Evaluating the Safety, Tolerability, and Pharmacokinetics of AMG 479 in Japanese Subjects with Advanced Solid Tumors	Ongoing
Monotherapy Study in Ewing's Family Tumors		
20060283	A Phase 2 Study of AMG 479 in Relapsed or Refractory Ewing's Family Tumors and Desmoplastic Small Round Cell Tumors	Ongoing
Combination Study in Mixed Solid Tumors		
20060134	A Phase 1b, Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetic of AMG 479 with Biologics or Chemotherapy in Adult Subjects with Advanced Solid Tumors	Ongoing
20070411	A Phase 1b/2 Open Label, Dose Escalation Study of AMG 655 in Combination With AMG 479 in Subjects With Advanced, Refractory Solid Tumors	Ongoing
Combination Study in Pancreatic Cancer		
20060323	A Phase 1b/2 Study to Evaluate the Safety and Efficacy of AMG 655 or AMG 479 in Combination With Gemcitabine as First-line Therapy for Metastatic Pancreatic Cancer	Ongoing

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Table 2. Clinical Studies With AMG 479 by Tumor Type

Protocol No.	Description	Status
Combination Study in Breast Cancer		
20060362	An International, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of AMG 479 with Exemestane or Fulvestrant in Postmenopausal Women with Hormone Receptor Positive Locally Advanced or Metastatic Breast Cancer	Ongoing
Combination Study in Ovarian Cancer		
20070080 (TRIO 014)	A Randomized, Double-blind, Placebo Controlled, Multi-center, Phase II Study of Adding AMG 479, a Fully Human Monoclonal Antibody Against IGF-1R to First Line Chemotherapy in Patients with Optimally Debulked (< 1 cm) Epithelial Ovarian Cancer.	Ongoing
20070834 (TRIO 015)	A Multicenter Open Label Phase II Study of the Efficacy and Safety of AMG 479, a Fully Human Monoclonal Antibody Against Insulin-like Growth Factor Type 1 Receptor (IGF-1R) as Second Line Therapy in Patients with Recurrent Platinum-sensitive Ovarian Cancer	Ongoing
Combination Study in Colorectal Cancer		
20060447	A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination with Panitumumab versus Panitumumab Alone in Subjects with Wild-Type KRAS Metastatic Colorectal Cancer	Ongoing
20060579	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	Ongoing
20070820	A Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin- or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab	Ongoing
Combination Study in Lung Cancer		
20060534	A Phase 1b/ 2 Trial of AMG 479 or AMG 102 in Combination with Platinum-based Chemotherapy as First-Line Treatment for Extensive Stage Small Cell Lung Cancer	Ongoing
20080257	A Phase 1b/ 2 Study of AMG 479 in Combination with Paclitaxel and Carboplatin for the First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer	Ongoing

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2.2.4 Safety and Efficacy Summary

Studies across multiple indications have been completed with conatumumab and AMG 479. Additional information about the safety and efficacy for both products is available in the current Investigator's Brochure.

2.3 Rationale

The purpose of this protocol is to allow continued treatment with conatumumab, with or without co-therapy, or AMG 479 therapy alone to subjects previously treated with conatumumab, with or without co-therapy, or with AMG 479 therapy alone, who have not progressed during that treatment.

2.4 Clinical Hypotheses

The purpose of this study is to provide a mechanism for subjects to continue to receive treatment with conatumumab and/or AMG 479.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2 multi-center, open-label study that permits subjects who have completed a separate Amgen-sponsored conatumumab or AMG 479 study to continue treatment with conatumumab, with or without co-therapy (chemotherapy with and without bevacizumab, or AMG 479), or with AMG 479 therapy alone. Subjects who have not progressed on a separate Amgen protocol are eligible to participate in this trial.

This study will only be conducted in centers that treated subjects in previous conatumumab or AMG 479 studies managed by Amgen Inc.

Subjects must have received conatumumab, with or without co-therapy, or AMG 479 therapy alone on the parent study.

In this extension study, conatumumab and AMG 479 study drugs will be administered at the same dose level and schedule that the subject received at the conclusion of the parent conatumumab or AMG 479 study, accommodating any subjects who were maintained on a reduced dose level or different schedule of administration in their parent study. At the discretion of the investigator, subjects who were receiving conatumumab monotherapy on the parent study may switch at the time of starting this study (and only at this time) to receive monotherapy at an extended dosing frequency, to a maximum of every 3 weeks, if the total weekly dose remains the same as for the parent study.

Subjects will be evaluated before every cycle of conatumumab or AMG 479 therapy at the study clinic. These study visits will include a standard of care clinical assessment which includes collection of vital signs, adverse events, concomitant medications, and laboratory samples and results. Radiological assessments to evaluate disease extent (with change compared to nadir from the parent protocol) should be performed at regular intervals, at a minimum once every 6 (± 1) months or more frequently if clinically

indicated (starting from their last scan on the parent protocol), per standard of care (SOC) at each facility.

Reasons for study discontinuation will include progressive disease, intolerance to investigational product(s), and/or need for additional systemic anticancer treatment. When a subject discontinues the study for any reason, a safety follow-up visit will be completed at least 30 (+3) days after the last dose of protocol-specified therapy. This visit will include a standard of care clinical assessment, vital sign measurements, laboratory tests for blood and urine, adverse event assessment, and concomitant medications assessment. Subjects will also be assessed for anti-conatumumab antibody (and anti-AMG 479 antibody, if the subject has received AMG 479) assessment 60 (±14) days after the last administration of protocol-specified therapy.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

The study will be conducted in study sites that treated subjects in previous conatumumab or AMG 479 studies in the United States, Europe, and possibly other countries. The number of sites will be determined by the number and location of subjects who transition into this study from the separate (parent) Amgen conatumumab or AMG 479 studies.

Sites that do not enroll subjects within 3 months of site initiation may be terminated.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

The sample size is dependent upon the number of subjects that transition into this study from separate Amgen conatumumab or AMG 479 studies. The sample size is estimated to be approximately 15 subjects.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The estimated duration of individual subject participation on this trial begins on the date the subject signs the informed consent for this study and ends when the subject completes their Day 60 (immunogenicity) Follow-up visit 60 (± 14) days after the last dose of protocol-specified therapy, unless the subject has started another anti-cancer

therapy or withdrawn consent. The exact duration of each subject's participation on study will vary depending on each subject's individual clinical response to treatment.

The end of study for each subject is defined as the date the subject withdraws consent from the study, completes or has the opportunity to complete the Day 60 follow-up visit or dies.

3.4.2 End of Study

The end of study will occur when all the subjects have completed or had the opportunity to complete the Day 60 Follow-up visit. Amgen reserves the right to terminate the study.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (sex, age, race, date, and outcome of the screening process (eg, enrolled into study, reason for ineligibility, or refused to participate).

Before any study-specific procedure, the appropriate signed and dated written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

4.1.1 Disease Related

101. To be enrolled in this study, subjects must be currently enrolled in a prior Amgen-sponsored conatumumab or AMG 479 study and are eligible according to the parent study to receive their next dose of conatumumab (with or without co-therapy), or AMG 479 alone

102. Subjects must have their eligibility assessed for this study and be enrolled within 30 days of their last treatment on the parent protocol

4.2 Exclusion Criteria

4.2.1 Disease Related

201. Discontinued from a conatumumab or AMG 479 study due to an adverse event, including intolerance to conatumumab or AMG 479, respectively

202. Subjects determined to have disease progression during their participation in the parent Amgen study

4.2.2 General

203. Woman or man with partner of childbearing potential not consenting to use adequate contraceptive precautions ie, double barrier contraceptive methods (eg, diaphragm plus condom), or abstinence during the course of the study and for 6 months after the last dose of protocol-specified therapy administration

204. Subject is pregnant or breast feeding, or planning to become pregnant within 6 months after the last dose of protocol-specified therapy administration

205. Male subject with a pregnant partner who is not willing to use a condom during treatment and for an additional 6 months after the last dose of protocol-specified therapy administration

206. Subject has previously entered this study

207. Subject will not be available for protocol-required study visits, to the best of the subject and investigator's knowledge

208. Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). The informed consent form must be signed and personally dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion before any study procedures specific for this study occur (procedures that are part of routine care are not considered study specific procedures).

A subject is considered enrolled once all eligibility criteria are met and the site has received an Enrollment Confirmation fax/email from Amgen. All subjects who enroll will be assigned a unique subject identification number by the Amgen study team; this unique subject ID will be obtained when the site study staff sends the completed Enrollment Confirmation Form to Amgen for review. The unique number will consist of 11 digits; digits 1 to 3 represent the last 3 digits of the protocol, 4 to 8 the site number, and 9 to 11 the subject number at the site. For example, the first subject enrolled at site 50505 for protocol 20101116 would be assigned 11650505001. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed.

All efforts should be made to ensure that subjects do not have an interruption of conatumumab or AMG 479 treatment, and combination therapy as appropriate, when transferring from the parent Amgen protocol to this protocol. Subjects should receive first dose of conatumumab, and applicable combination therapy if any, or AMG 479 alone, according to the schedule on the parent protocol (interval includes cycle frequency plus dose delays due to toxicities). If for any reason, the subject is not able to

continue their treatment per their prior schedule, Amgen approval should be obtained prior to dosing.

6. TREATMENT PROCEDURES

Conatumumab and AMG 479 will be the only Investigational Products (IPs) administered in this study.

Subjects will receive the same regimen they were receiving at the conclusion of their parent Amgen-sponsored study. If 1 or more co-therapy drugs were permanently discontinued or dose-reduced on the parent study, their resumption or re-escalation will not be allowed on this study for that particular subject. If a co-therapy is only being temporarily held on the parent protocol, resuming it will be allowed according to standard of care guidelines.

Dose adjustments for subjects receiving treatment have been adapted from the parent protocols.

6.1 Conatumumab

Conatumumab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Refer to the Investigational Product Instruction Manual for details regarding packaging, labeling, storage, and dispensing of conatumumab.

6.1.1 Conatumumab Dosage, Administration, and Schedule

The starting dose and frequency of conatumumab will be determined based on the dose and frequency administered during the parent study.

Conatumumab will be administered by IV infusion through a peripheral line or indwelling catheter with an infusion set-up. In-line filter is not required. The dose of conatumumab will be calculated based on the subject's actual body weight during the study day 1 assessment and the dose must be recalculated if actual body weight changes by ± 10%. Investigators may recalculate the doses more frequently based on institutional guidelines.

If a subject misses a conatumumab dose, the dose will not be made up at a later date and the subject will remain on the original dosing schedule.

Conatumumab preparation will be administered by an IV infusion over a 60 (± 15) minutes period. If the dose administration was well tolerated during the parent protocol, administrations may be made over a 30 (± 10) minutes infusion period. Infusion time

can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion.

Conatumumab should not be mixed with, or administered as an infusion simultaneously with other medicinal products. An experienced and qualified staff member will perform the placement of the IV access, establishment of an IV line, and administration of the investigational product. The infusion line should be flushed with at least 5.0 mL of 0.9% normal saline or 5% dextrose before and after the investigational product administration to avoid mixing with other drug products or IV solutions. Conatumumab should not be administered as an IV push injection. If the investigational product extravasates during the IV administration, the infusion must be stopped immediately. The subject may develop a reddened area around the site of the infiltration, which is caused by accumulation of the investigational product in the surrounding tissues (ie, depot effect). A physician or medical staff involved in study evaluation must be available during the administration of the investigational product to assess and treat adverse events that may arise during dosing. Subjects will be monitored in the clinic throughout their infusion for any signs of adverse events and for at least 60 minutes after their infusion if previous doses of conatumumab were not well tolerated.

The date, start and end times, and volume of each conatumumab infusion (volume of conatumumab plus volume of diluent) will be recorded in the subject's medical record and electronic case report form (eCRF). Refer to the Investigational Product Instruction Manual for details regarding packaging, labeling, storage, preparation and dispensing of conatumumab.

6.1.1.1 Subjects Receiving Conatumumab in Monotherapy

Subjects currently receiving conatumumab monotherapy will continue doing so at the same dose. The dose range in the parent protocols is from 0.3 mg/kg Q2W to 15 mg/kg Q3W. Subjects will be allowed to switch from a Q2W dosing to a Q3W dosing if they so desire and their physician is in agreement, but only at the start of this study. In this case, the actual dose to be administered every 3 weeks will be recalculated in order to deliver the same weekly dose, according to the formula:

Q3W dose (in mg/kg) = Q2W dose (in mg/kg) x 1.5

Such change in dosing frequency should be communicated to Amgen's study team.

6.1.1.2 Subjects Receiving Conatumumab in Combination With AMG 479 (Transferring From Parent Protocol 20070411)

Subjects transitioning from the 20070411 protocol will continue receiving AMG 479 18 mg/kg Q3W in combination with conatumumab at 1, 3, or 15 mg/kg Q3W.

Conatumumab should be given on day 1 of each cycle after completion of the AMG 479 infusion, unless otherwise specified, allowing 30 minutes between the end of the AMG 479 infusion and the start of the conatumumab infusion to assess potential toxicities from AMG 479. If no toxicities were observed with previous doses, the time interval between the AMG 479 infusion and the conatumumab infusion will be at the Investigator's discretion.

6.1.1.3 Subjects Receiving Conatumumab in Combination With mFOLFOX6 and Bevacizumab (Transferring From Parent Protocol 20060464)

All subjects will be treated with mFOLFOX6 and bevacizumab on each of the 14 day (+ 3 days) treatment cycles before infusion of conatumumab (2 or 10 mg/kg Q2W, based on their dose from study 20060464).

mFOLFOX6 and bevacizumab will be obtained by each center from commercial sources. Study personnel will follow the institutional standard operating procedures for handling mFOLFOX6 and bevacizumab. For additional detail and full prescribing information please see the most recent local version of the label for the products.

6.1.2 Conatumumab Premedication

This section applies to all subjects, irrespective of whether they are receiving conatumumab in monotherapy or in combination with AMG 479 or chemotherapy.

No specific premedication is required for routine conatumumab infusions. If during or after any infusion a reaction occurs, pre-medication may be used for subsequent conatumumab infusions. Subjects, who experience any serious infusion reaction (eg, dyspnea, chest tightness, fever, rigors or hypotension) during conatumumab administration will have the infusion stopped. Continuation of drug administration will be based on the severity and resolution of the event and will be at the discretion of the investigator. Treatment for an infusion reaction may include methylprednisolone, ranitidine, diphenhydramine, atropine, epinephrine, or other drugs, depending on the severity of the reaction. Premedication (eg, antihistamines or corticosteroids) may be considered for subsequent administrations in subjects who develop an infusion reaction, at the discretion of the investigator. Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be followed for safety.

6.1.3 Conatumumab Toxicity Management

This section applies to all subjects, irrespective of whether they are receiving conatumumab in monotherapy or in combination with AMG 479 or chemotherapy.

Subjects should be assessed clinically for toxicity before each dose using the National Cancer Institute (NCI) CTCAE version 3.0 (Appendix B). Complete blood count with differential and chemistry panels including glucose and liver function laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) must be obtained ≤ 3 days before the dose of conatumumab on Day 1 of each cycle, and the results must be checked before each treatment. Amylase and Lipase values must be obtained at every cycle thereafter as close as possible to the scheduled dosing date. Dosing will occur only if these test values are acceptable per protocol guidelines (see Sections 6.1.3.1 to 6.1.3.4).

Any adverse event deemed related to conatumumab requiring a dose hold of more than 42 days will result in conatumumab being permanently discontinued.

If conatumumab administration does not commence within 3 days of the per protocol administration date due to an adverse event deemed related to conatumumab, the dose will be considered a missed dose, and conatumumab administration may resume at the next planned dosing date if the criteria outlined below are met. A missed dose will not be made up.

If an unscheduled interruption of conatumumab administration occurs, not due to toxicity events, the study site personnel should notify the sponsor at the earliest possible time.

There will be no conatumumab dose reductions or escalations in this study.

6.1.3.1 ALT or AST Elevations

The rules for conatumumab dosing interruptions in response to ALT and AST elevations are provided in Table 3.

Table 3. Conatumumab Dose Interruption Guidelines for Increases in ALT and AST Levels

AST or ALT Elevation	Conatumumab dose	Outcome	Conatumumab Dose Modification
Grade 1 or 2	No change	-	No change
Grade 3 or 4[a]	Hold	Improve to ≤ Grade 1 or baseline	Restart full dose
		No improvement [b]	Discontinue

[a] Not related to conatumumab. Conatumumab should be withheld if the change in AST/ALT is > 5 x ULN and ≤ 10 x ULN, and is related to conatumumab. Conatumumab should be discontinued if the change in AST/ALT is > 10 x ULN and is related to conatumumab.
[b] No improvement to ≤ Grade 1 or the subject's baseline within 28 days of onset.
ALT = alanine aminotransferase, AST = aspartate aminotransferase

Subjects who develop conatumumab-related elevation of either AST or ALT > 10 ULN will permanently discontinue conatumumab.

For subjects who develop an AST or ALT elevation related to conatumumab which does not require discontinuation of investigational product (ie, AST/ALT elevation > 5 x ULN and ≤ 10 x ULN), treatment with conatumumab will be withheld until the level of ALT or AST has returned to grade ≤ 1 or the subject's baseline within 28 days of onset as described in Table 3.

Attribution to conatumumab for the abnormal liver function test criteria in the context of oncology patients needs to be considered carefully. There should be no evidence of obstruction, such as elevated alkaline phosphatase in gall bladder or bile duct disease, progression of malignancy, or other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs).

6.1.3.2 Serum Amylase or Lipase Elevation

Amylase and lipase values must be obtained at every cycle as close as possible to the scheduled dosing date. Before conatumumab administration the investigator or designee will review the subject's previous amylase and lipase values and will follow the dose interruption guidelines in Table 4 to determine treatment suitability. Results from present cycle's amylase and lipase tests are not required to be available prior to dosing. The investigator can use previous cycle's amylase and lipase values if present cycle's results are not available before dosing. Dosing modifications based on present cycle's amylase and/or lipase values will apply to the next treatment cycle.

Table 4. Conatumumab Product Dose Interruption Guidelines for Increases in Serum Amylase or Lipase Levels

Amylase or Lipase Elevation	Conatumumab dose	Outcome	Conatumumab Dose Modification
Grade 1, 2 or 3‡	No change	-	No change
Grade 4[a]	Hold	Improve to ≤ Grade 2 or baseline	Restart full dose
		No improvement [b]	Discontinue

‡ Results from present cycle's amylase and lipase tests are not required to be available prior to dosing. The investigator can use previous cycle's amylase and lipase values if present cycle results are not available before dosing. Dosing modifications based on present cycle's amylase and/or lipase values will apply to the next treatment cycle.
[a] Conatumumab must be discontinued if a Grade 4 event is related to conatumumab persists for > 28 days.
[b] No improvement to ≤ Grade 2 or the subject's baseline within 28 days of onset.

Subjects experiencing Grade 4 elevation of amylase and/or lipase related to conatumumab will have conatumumab withheld and serum amylase and lipase monitored until the amylase and/or lipase values resolve to Grade ≤ 2 or the subject's baseline.

Any Grade 4 amylase or lipase elevation deemed related to conatumumab requiring a dose hold of more than 28 days will result in conatumumab being permanently discontinued.

6.1.3.3 Non-hematologic Toxicities

Any Grade 3 or higher non-hematologic adverse event (other than AST, ALT, lipase or amylase elevation) deemed related to conatumumab will result in conatumumab being withheld until symptoms resolve to ≤ Grade 1 or subject's baseline within 28 days of onset. Exceptions to this rule are anorexia, nausea, vomiting, stomatitis/mucositis, diarrhea, fatigue, and pulmonary embolism that will lead to conatumumab being withheld only if following criteria are met:

- Grade 3 or higher anorexia, nausea, vomiting, stomatitis/mucositis, or diarrhea not manageable despite maximum supportive care
- Grade 3 fatigue persists more than 7 days
- Symptomatic pulmonary embolism (incidental asymptomatic pulmonary embolism or deep vein thrombosis will not lead to conatumumab being withheld)

Any Grade 3 or higher non-hematologic adverse event (other than AST, ALT, lipase or amylase elevation) as defined above deemed related to conatumumab requiring a dose hold of more than 28 days will result in conatumumab being permanently discontinued.

6.1.3.4 Hematologic Toxicities

Any Grade 3 or higher hematologic adverse event deemed related to conatumumab will result in conatumumab being withheld until symptoms resolve to ≤ Grade 1 or subject's baseline with 28 days of onset. Exceptions to this rule are anemia, neutropenia, and thrombocytopenia that will lead to conatumumab being withheld only if following criteria are met:

- Grade 4 anemia
- Grade 3 or 4 neutropenia with fever > 38.5°C
- Grade 4 neutropenia or thrombocytopenia > 7 days

Any Grade 3 or higher hematologic adverse event deemed related to conatumumab requiring a dose hold of more than 28 days as defined above will result in conatumumab being permanently discontinued.

6.2 AMG 479

AMG 479 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study distribution procedures. **Upon the appropriate approvals being received, AMG 479 will be manufactured and packaged by Amgen, and labelled and distributed by NantCell using NantCell clinical study distribution procedures. Subsequent to this, and subject to the appropriate approvals being in place, AMG 479 will be manufactured, packaged, labelled, and distributed by NantCell, using NantCell clinical study distribution procedures.** Refer to the Investigational Product Instruction Manual for details regarding packaging, labeling, storage, and dispensing of AMG 479.

6.2.1 AMG 479 Dosage, Administration, and Schedule

The starting dose and frequency of AMG 479 will be determined based on the dose and frequency administered during the parent study.

The dose (infusion volume) of AMG 479 will be calculated based on the subject's actual body weight during the study day 1 assessment. The dose will not need to be recalculated unless the actual body weight changes by ± 10%. Investigators may recalculate the dose of AMG 479 more frequently according to institutional guidelines.

AMG 479 will be administered by IV infusion through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding filter with a 0.2- or 0.22-micron pore size in-line filter infusion set-up.

AMG 479 will be administered by an IV infusion over a 60 (± 15) minutes period. If the dose administration was well tolerated during the parent study, AMG 479 may be given over 30 (± 10) minutes. Infusion times can be extended to a maximum of 120 minutes for subjects deemed unable to tolerate the 60 minutes infusion.

AMG 479 should not be mixed with, or administered as an infusion simultaneously with other medicinal products. The infusion line should be flushed with at least 5.0 mL of 0.9% normal saline before and after the investigational product administration to avoid mixing with other drug products or IV solutions. AMG 479 should not be administered as an IV push injection.

If the AMG 479 extravasates during the IV administration, the infusion must be stopped immediately. The subject may develop a reddened area around the site of the infiltration, which is caused by accumulation of AMG 479 in the surrounding tissues (ie, depot effect).

An experienced and qualified staff member will perform the placement of the IV access, establishment of an IV line, and administration of the investigational product. A physician or medical staff involved in study evaluation must be available during the administration of the investigational product to assess and treat adverse events that may arise during dosing. If previous doses were well tolerated, subsequent post-infusion monitoring is not required.

Date, start and end times, and volume of each AMG 479 infusion (volume of AMG 479 plus volume of diluent) will be recorded in the subject's medical record and eCRF.

Refer to the AMG 479 Investigational Product Instruction Manual for details regarding packaging, labeling, storage, preparation and dispensing of AMG 479.

6.2.1.1 AMG 479 Dosage and Schedule (for Subjects Transferring From Protocol 20070411)

Subjects previously enrolled in Study 20070411 will receive conatumumab and/or AMG 479 per parent protocol. AMG 479 18 mg/kg will be administered IV Q3W, unless discontinued during treatment on parent protocol. There will be no individual AMG 479 dose reductions, except as outlined below in Table 5, Thrombocytopenia without Bleeding.

If no toxicities were observed during the infusion period on the parent study, the time interval between the AMG 479 infusion and the conatumumab infusion for subsequent cycles will be at the investigator's discretion. If toxicities were observed during the

infusion period on the parent study, allow 30 minutes between the end of the AMG 479 infusion and the start of the conatumumab infusion to assess potential toxicities from AMG 479.

6.2.1.2 AMG 479 Dosage and Schedule (for Subjects Transferring From Protocol 20050118)

Subjects previously enrolled in Study 20050118 will receive AMG 479 monotherapy per parent protocol. AMG 479 20 mg/kg will be administered IV Q3W. At the discretion of the investigator, subjects who have been on the parent study for more than 48 months without progression or unacceptable toxicity may continue receiving AMG 479 on an extended dosing frequency, to a maximum of Q4W (± 3 days). Once the extended dosing frequency is selected, the dosing schedule must remain the same throughout the study. There will be no individual AMG 479 dose reductions, except as outlined below in Table 5, Thrombocytopenia without Bleeding.

6.2.2 AMG 479 Premedication

No specific premedication is required for routine AMG 479 infusions. If during or after any infusion a reaction occurs, pre-medication may be used for subsequent AMG 479 infusions. Subjects, who experience any serious infusion reaction (eg, dyspnea, chest tightness, fever, rigors or hypotension) during AMG 479 administration will have the infusion stopped. Continuation of drug administration will be based on the severity and resolution of the event and will be at the discretion of the investigator. Treatment for an infusion reaction may include methylprednisolone, ranitidine, diphenhydramine, atropine, epinephrine, or other drugs, depending on the severity of the reaction. Premedication (eg, antihistamines or corticosteroids) may be considered for subsequent administrations in subjects who develop an infusion reaction, at the discretion of the investigator. Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be followed for safety.

6.2.3 AMG 479 Toxicity Management

This section applies subjects receiving AMG 479 alone or in combination with conatumumab.

6.2.3.1 General Criteria

The NCI CTCAE v3.0 grading scale (Appendix B) will be used as a guide for grading adverse events. All adverse events will be documented on the adverse event eCRF.

If AMG 479 is held due to AMG 479 related toxicities, conatumumab should also be held if administered in combination with AMG 479, in accordance with protocol guidelines

(Table 5 and Table 6). In the event AMG 479 is held for more than 42 days for related toxicity, AMG 479 will be permanently discontinued. Treatment with conatumumab should continue Q3W after AMG 479 has been discontinued due to AMG 479 related toxicity. In the event that treatment with conatumumab is discontinued for any reason prior to disease progression, AMG 479 treatment should continue. If conatumumab has been permanently discontinued and/or AMG 479 is the only agent administered, in case of AMG 479-related toxicities AMG 479 treatment should be delayed by 1 week interval(s) until recovery, in accordance with protocol guidelines. Subjects missing ≥ 2 consecutive scheduled administrations of AMG 479, not due to AMG 479 related toxicity, must have the case reviewed by the Amgen Medical Director to determine if this subject can resume AMG 479. A missed dose of AMG 479 will not be made up.

6.2.3.2 Dosing Adjustments of AMG 479 Alone or AMG 479 in Combination with Conatumumab

Subjects should be assessed clinically for toxicity prior to administration of protocol-specified treatment using the CTCAE v3.0 grading scale (Appendix B). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) and glucose must be obtained ≤ 3 days before the first dose of protocol-specified treatment on day 1 of each cycle, and the results must be evaluated before each planned infusion. Dosing will occur only if these test values are acceptable, as outlined below (Table 5 and Table 6).

In addition to dosage adjustments and dose delays, toxicities will be managed according to local institutional and all other applicable guidelines. If multiple or overlapping toxicities occur, the most stringent dose modification criteria must be followed.

There will be no intra-subject dose reductions or escalations for conatumumab. There will be no individual AMG 479 dose reductions, except as outlined below in Table 5 for thrombocytopenia without bleeding.

Table 5. Conatumumab and AMG 479 Dosing Modifications for Hematologic Toxicity Based on Hematology Counts ≤ 3 Days Prior to a New Cycle

Toxicity	Action to be taken
Thrombocytopenia WITHOUT Bleeding	
Thrombocytopenia Grade ≤ 2	No AMG 479 or conatumumab dosing modifications
Thrombocytopenia Grade 3 [b]	Delay AMG 479 and conatumumab by 1 week interval(s) until recovery to grade ≤ 2, or ≤ baseline (+ 10%). [a] AMG 479 First episode: If thrombocytopenia is deemed related to AMG 479, then permanently dose reduce AMG 479 by 50%. Second and subsequent episodes: No further dose reductions of AMG 479 will occur; resume AMG 479 at the investigator's discretion. Conatumumab Resume previous dose. If conatumumab is the only agent administered, then resumption of conatumumab treatment is at the investigator's discretion.
Thrombocytopenia Grade 4 [b]	Delay AMG 479 and conatumumab by 1 week interval(s) until recovery to grade ≤ 2, or ≤ baseline (+ 10%). [a] AMG 479 First episode: Permanently dose reduce AMG 479 by 50%. [b] Second and subsequent episodes: Permanently discontinue AMG 479. Conatumumab Resume previous dose. Permanently discontinue conatumumab if grade 4 thrombocytopenia is deemed related to conatumumab or to the combination of conatumumab with AMG 479 and lasts > 7 days. If conatumumab is the only agent administered, then - resumption of conatumumab treatment is at the investigator's discretion; - permanently discontinue conatumumab if grade 4 thrombocytopenia lasts > 7 days.

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The CTCAE v3.0 grading scale (Appendix B) will be used for grading toxicity.
[a] conatumumab and/or AMG 479 will be permanently discontinued if held for more than 42 days due to related toxicity.
[b] Subjects on therapeutic anticoagulation treatment (eg, full dose coumadin or low molecular weight heparin) while receiving AMG 479, who develop concurrent grade 3 or 4 thrombocytopenia will permanently discontinue AMG 479.
[c] Exceptions:
(i) except lymphocytopenia
(ii) except anemia
(iii) neutropenia only if grade 3 or 4 with fever > 38.5°C, or if grade 4 > 7 days

Table 5. Conatumumab and AMG 479 Dosing Modifications for Hematologic Toxicity Based on Hematology Counts ≤ 3 Days Prior to a New Cycle

Toxicity	Action to be taken
Thrombocytopenia WITH Bleeding	
Thrombocytopenia Grade 1	No conatumumab or AMG 479 dosing modifications
Thrombocytopenia Grade 2	Delay AMG 479 and conatumumab by 1 week interval(s) until recovery from bleeding, then resume previous doses of AMG 479 and of conatumumab. [a] AMG 479 Permanently discontinue AMG 479. Conatumumab Delay conatumumab by 1 week interval(s) until recovery from bleeding [a], then resume previous dose Permanently discontinue conatumumab in case of grade ≥ 3 thrombocytopenia with grade > 1 bleeding related to conatumumab or to the combination of conatumumab with AMG 479. Permanently discontinue conatumumab, if conatumumab is the only agent administered.
Thrombocytopenia Grade ≥ 3 [b]	
Any Other Hematologic Toxicity [c]	
Grade ≤ 2	No AMG 479 or conatumumab dosing modifications
Grade ≥ 3	First episode: Delay AMG 479 and/or conatumumab by 1 week interval(s) until recovery to ≤ grade 2, or ≤ baseline (+ 10%), then resume previous doses of AMG 479 and of conatumumab. [a, c] Second and subsequent episodes of the same event: Delay AMG 479 and conatumumab by 1 week interval(s) until recovery to ≤ grade 2 or ≤ baseline (+ 10%). [a, c] AMG 479 Permanently discontinue AMG 479 in case of recurrent grade ≥ 3 hematologic toxicity related to AMG 479. [c] Conatumumab Permanently discontinue conatumumab in case of recurrent grade ≥ 3 hematologic toxicity related to conatumumab or to the combination of conatumumab with AMG 479. [c]

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The CTCAE v3.0 grading scale (Appendix B) will be used for grading toxicity.

[a] conatumumab and/or AMG 479 will be permanently discontinued if held for more than 42 days due to related toxicity.

[b] Subjects on therapeutic anticoagulation treatment (eg, full dose coumadin or low molecular weight heparin) while receiving AMG 479, who develop concurrent grade 3 or 4 thrombocytopenia will permanently discontinue AMG 479.

[c] Exceptions:
(i) except lymphocytopenia
(ii) except anemia
(iii) neutropenia only if grade 3 or 4 with fever > 38.5°C, or if grade 4 > 7 days

Table 6. Conatumumab and AMG 479 Dosing Modifications for Non-hematologic Toxicity Based on Toxicity ≤ 3 Days Prior to a New Cycle

Toxicity	Action to be taken
Serum Amylase or Lipase Elevations [‡]	
Grade ≤ 3	No AMG 479 or conatumumab dosing modifications
Grade 4	Delay AMG 479 and/or conatumumab by 1 week interval(s) until recovery to grade ≤ 2, or ≤ baseline (+ 10%), then resume previous doses of AMG 479 and of conatumumab. [a] Permanently discontinue conatumumab if grade 4 amylase or lipase elevation persists > 7 days.
Hepatotoxicity: Serum AST or ALT Elevations	
Grade 1 or 2 (≤ 5 x ULN)	No AMG 479 or conatumumab dosing modifications
Grade 3 or 4 (> 5 x ULN)	Delay AMG 479 and/or conatumumab by 1 week interval(s) until recovery to grade ≤ 2 or ≤ baseline (+ 10%), then resume previous doses of AMG 479 and of conatumumab [a] AMG 479 Permanently discontinue AMG 479 in case of recurrent grade ≥ 3 toxicity related to AMG 479; or if AST or ALT is > 10 x ULN related to AMG 479. Conatumumab Permanently discontinue in case of recurrent grade ≥ 3 toxicity related to conatumumab; or if AST or ALT is > 10 x ULN related to conatumumab.
Hyperglycemia (Glucose Elevations)	
Grade ≤ 2	No AMG 479 and conatumumab dosing modifications [c]

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The CTCAE v3.0 grading scale (Appendix B) will be used for grading toxicity.

[‡] Results from amylase and lipase tests are not required to be available prior to dosing. The investigator can use previous cycle's amylase and lipase values if present cycle results are not available before dosing. Dosing modifications based on present cycle's amylase and/or lipase tests will apply to the next treatment cycle.

[a] conatumumab and/or AMG 479 will be permanently discontinued if held for more than 42 days due to related toxicity.

[c] Manage hyperglycemia per local institutional guidelines.

[d] Exceptions: The following adverse events do not require dosing modifications, unless:
(i) Grade 3 fatigue persists for > 7 days, or grade 4 fatigue; [b]
(ii) Grade 3 or 4 anorexia, nausea, vomiting, stomatitis/mucositis or diarrhea despite maximum supportive care; [b]
(iii) Symptomatic pulmonary embolism. [b]

[e] Refer to Table 5 for management of Grade ≥ 2 infection in the presence of neutropenia (ANC < 1.5 x 10^9/L) at any time.

Table 6. Conatumumab and AMG 479 Dosing Modifications for Non-hematologic Toxicity Based on Toxicity ≤ 3 Days Prior to a New Cycle

Toxicity	Action to be taken
Grade ≥ 3	If hyperglycemia is deemed related to AMG 479, delay AMG 479 and conatumumab by 1 week interval(s) until hyperglycemia resolves to grade ≤ 2, or ≤ baseline (+ 10%), then resume full dose [a, c] Permanently discontinue AMG 479 in case of - recurrent grade 4 hyperglycemia related to AMG 479 [c, d]; or - hyperglycemia with life-threatening consequences (ketoacidosis or hyperosmolar non-ketotic coma). [c] Permanently discontinue conatumumab in case of hyperglycemia with life-threatening consequences (ketoacidosis or hyperosmolar non-ketotic coma), if deemed related to conatumumab, or if conatumumab is the only agent administered. [c]
Any Other Non-Hematologic Toxicity (other than infusion reactions and hearing loss)	
Grade ≤ 2	No AMG 479 and/or conatumumab dosing modifications [e]
Grade 3	Delay AMG 479 and/or conatumumab by 1 week interval(s) until recovery to grade ≤ 2, or ≤ baseline (+ 10%), then resume full dose of AMG 479 and of conatumumab. [a, d, e]
Grade 4	First episode: Delay AMG 479 and/or conatumumab by 1 week interval(s) until recovery to grade ≤ 2, or ≤ baseline (+ 10%), then resume previous doses of AMG 479 and of conatumumab. [a,d,e] Second and subsequent episodes of the same event: Delay AMG 479 and/or conatumumab by 1 week interval(s) until recovery to grade ≤ 2, or ≤ baseline (+ 10%), then resume previous doses of AMG 479 and/or of conatumumab. [a,d,e,] AMG 479 Permanently discontinue AMG 479 in case of recurrent grade ≥ 3 non-hematologic toxicity related to AMG 479. [d,e] Conatumumab Permanently discontinue conatumumab in case of recurrent grade ≥ 3 non-hematologic toxicity related to conatumumab. [d,e]

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The CTCAE v3.0 grading scale (Appendix B) will be used for grading toxicity.

[‡] Results from amylase and lipase tests are not required to be available prior to dosing. The investigator can use previous cycle's amylase and lipase values if present cycle results are not available before dosing. Dosing modifications based on present cycle's amylase and/or lipase tests will apply to the next treatment cycle.

[a] conatumumab and/or AMG 479 will be permanently discontinued if held for more than 42 days due to related toxicity.

[c] Manage hyperglycemia per local institutional guidelines.

[d] Exceptions: The following adverse events do not require dosing modifications, unless:
(i) Grade 3 fatigue persists for > 7 days, or grade 4 fatigue; [b]
(ii) Grade 3 or 4 anorexia, nausea, vomiting, stomatitis/mucositis or diarrhea despite maximum supportive care; [b]
(iii) Symptomatic pulmonary embolism. [b]

[e] Refer to Table 5 for management of Grade ≥ 2 infection in the presence of neutropenia (ANC < 1.5 x 10^9/L) at any time.

6.2.3.3 AMG 479 Related Non-hematologic Adverse Events (Excluding Hyperglycemia and Elevation of Transaminases)

Any grade 4 non-hematologic adverse event (except grade 4 hyperglycemia, and transaminase elevations, as discussed below) deemed related to AMG 479 will result in the permanent discontinuation of AMG 479. Subjects who are diagnosed with a symptomatic pulmonary embolism on study treatment must permanently discontinue AMG 479. Subjects who are diagnosed with an asymptomatic pulmonary embolism, which has been incidentally diagnosed by CT or other imaging modality, must be managed per local regional guidelines and can remain on study treatment at the discretion of the investigator (see Section 6.2.3.4 for on study anti-coagulation management guidelines).

Any grade 3 non-hematologic adverse event deemed related to AMG 479 will result in AMG 479 being withheld until symptoms resolve to grade ≤ 1 or to the subject's baseline grade.

6.2.3.4 Anti-coagulation Management

Subjects requiring initiation of therapeutic anti-coagulation treatment while on study treatment (eg, for deep venous thrombosis or asymptomatic pulmonary embolism) will have AMG 479 and/or conatumumab withheld until the therapeutic anti-coagulation treatment is stable (eg, on coumadin with an INR of 2 to 3 for at least 14 days). Subjects who remain on full dose low molecular heparin (without Coumadin) as therapeutic anti-coagulation may restart AMG 479 and/or conatumumab at the discretion of the investigator.

Subjects on therapeutic anti-coagulation treatment while being treated with AMG 479 who develop concurrent grade 3 or 4 thrombocytopenia regardless of relationship to AMG 479 will permanently discontinue AMG 479.

6.2.3.5 AMG 479 Related Infusion Reactions

Investigational product pre-medication is not required for routine infusions. Investigators should monitor subjects for signs and symptoms of infusion reactions. Any subject who experiences a grade 4 infusion reaction must permanently discontinue AMG 479. Subjects, who experience a grade 3 infusion reaction during AMG 479 administration, will have the AMG 479 infusion stopped and the remainder of that AMG 479 infusion will not be administered. Continuation of subsequent AMG 479 dosing after a grade 3 infusion reaction will be based on the severity and resolution of the event, and the

grade 3 infusion reaction must be reviewed by the Amgen medical monitor to determine if the subject can resume AMG 479.

If an AMG 479 infusion is interrupted because of a grade 1 or 2 infusion reaction, the infusion may be restarted after resolution of the event and stabilization of the subject, with total infusion time up to 120 minutes. If a subject is unable to complete an AMG 479 infusion on the day of the infusion due to an infusion reaction, then the remainder of the infusion will not be made up on subsequent days.

At the discretion of the investigator, treatment for an infusion reaction may include solumedrol (50 to 80 mg IV bolus or equivalent), ranitidine 50 mg IV bolus (or equivalent), diphenhydramine 50 mg IV bolus (or equivalent). AMG 479 pre-medications are recommended for subjects who have previously experienced an AMG 479 related infusion reaction. The AMG 479 pre-medication that will be used is at the discretion of the investigator; however, it is recommended that the investigator consider using any of the following AMG 479 pre-medication for future infusions: dexamethasone or solumedrol, ranitidine, diphenhydramine or equivalents. Investigational product pre-medications must be recorded in the eCRF. Subjects treated with steroids while on study should be monitored closely for hyperglycemia, as the combination of steroids and AMG 479 may increase this risk.

Investigators should decrease the AMG 479 infusion rate by 50% (eg, increase the AMG 479 infusion duration from 30 to 60 minutes) in subjects who have previously had a grade 3 AMG 479 infusion reaction. For subjects who have had a grade 1 or 2 AMG 479 infusion reaction, decreasing the AMG 479 infusion rate is at the discretion of the investigator. Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be followed for safety.

6.2.3.6 AMG 479 Hearing Loss

Subjects experiencing hearing loss will be managed as per local regional medical guidelines. If hearing loss cannot be clearly attributed to another cause (eg, acoustic trauma), investigators should permanently discontinue AMG 479 in subjects who experience severe (≥ grade 3) hearing loss.

6.2.4 Bisphosphonates

Bisphosphonates (eg, pamidronate or zoledronic acid) may be used in subjects with documented bone metastases, according to standard of care, the most recent version of

the label for the product, in the region in which it is approved, and all applicable guidelines.

6.3 Subjects Receiving Conatumumab in Combination With mFOLFOX6/Bevacizumab (Transferring From Parent Protocol 20060464)

Subjects transitioning from the 20060464 study who are on mFOLFOX6/bevacizumab in combination with conatumumab will continue to receive the same regimen with the same doses and timing. The components of the mFOLFOX6 regimen and bevacizumab will be administered per standard of care, according to the PI's clinical judgment and institutional guidelines.

All other protocol-required drugs including, mFOLFOX6 and bevacizumab, that are commercially available are not provided by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these drugs.

All subjects will be treated with mFOLFOX6 and bevacizumab on each of the 14 day (+ 3 days) treatment cycle before infusion of conatumumab.

6.3.1 mFOLFOX6 Regimen

Modified FOLFOX6 regimen is a combination therapy of oxaliplatin (85 mg/m^2) administered as a 2-hour infusion on day 1; leucovorin (400 mg/m^2 racemate or 200 mg/m^2 levo-leucovorin) administered as a 2-hour infusion on day 1; followed by a loading dose of 5-FU (400 mg/m^2) IV bolus administered on day 1, then 5-FU (2,400 mg/m^2) via ambulatory pump administered for a period of 46-48 hours every 14 days (+ 3 days).

Administration of mFOLFOX6 chemotherapy will commence on day 1 of each treatment cycle and end with a continuous IV infusion of 5-FU. For the purpose of this protocol, the administration of continuous IV infusion of 5 FU will commence after conatumumab infusions.

A new cycle of mFOLFOX6 treatment will be repeated every 2 weeks (+ 3 days) but may not be administered to the subject if the ANC < 1.0 x 10^9 cells/L; or if the platelet count is < 75 x 10^9/L; if stomatitis, or diarrhea have not recovered to ≤grade 1; or if fatigue has not recovered to ≤ grade 2. Up to a 6 week delay is allowed in the initiation of a new cycle of treatment for resolution of toxicities. A treatment delay of one component of the mFOLFOX6 regimen (ie, 5-FU/leucovorin or oxaliplatin) results in a similar delay of the other component to allow both therapies to be given together on day 1 of each 2-week cycle. Any delay to the start of mFOLFOX6 or bevacizumab will result in the same delay

to the bevacizumab and conatumumab so that all treatments are given together. Study procedures associated with each cycle of therapy will also be delayed accordingly. If conatumumab is held due to toxicities, mFOLFOX6 and bevacizumab should continue as planned and the conatumumab will be restarted at the next cycle of chemotherapy, so long as the toxicities have reduced in accordance with protocol guidelines.

If parameters are not met by the scheduled dosing date, blood tests and/or clinical evaluations should occur at least weekly to monitor these parameters. The guideline in Section 6.3.2 will be followed for mFOLFOX6/bevacizumab delay and dosing resumption.

In the event that mFOLFOX6 chemotherapy or any of its components administration is permanently discontinued for any reason prior to disease progression, bevacizumab and conatumumab may continue. Investigational product infusions should remain on a once every 14 days (+ 3 days) schedule until the subject develops disease progression or is unable to tolerate conatumumab.

If mFOLFOX6 chemotherapy interruption is ≤ 6 weeks from the previous cycle, and the subject has recovered from toxicity, as specified above, and the subject's disease has not progressed, mFOLFOX6 chemotherapy should be restarted at doses according to Table 7, Table 8, and Table 9. If mFOLFOX6 chemotherapy interruption is > 6 weeks, but the subject has recovered from toxicity and the subject's disease has not progressed, the case should be reviewed by the sponsor study team in conjunction with the investigator to determine the appropriateness of treatment resumption.

6.3.1.1 mFOLFOX6 Regimen Premedication

5-FU and oxaliplatin may be emetogenic. Prior to the administration of mFOLFOX6, pre-medication with antiemetics, such as serotonin ($5HT_3$) antagonists (ie, ondansetron, or granisetron) with or without dexamethasone may be used at the investigator's discretion or according to institutional standards.

6.3.1.2 mFOLFOX6 Dose Levels

Subjects should be closely monitored for mFOLFOX6 toxicity. Doses of 5-FU and oxaliplatin may be adjusted depending on an individual subject's tolerance. The dose of leucovorin will remain fixed at 400 mg/m^2 racemate (d,l-leucovorin), or 200 mg/m^2 l-leucovorin). Table 7, Table 8, and Table 9 indicate recommended dose levels and modification guidelines for oxaliplatin and 5-FU for non-neurological and neurological toxicity.

6.3.2 mFOLFOX6 Dose Modification

Table 7 describes the recommended dose reductions for non-neurological toxicity.

Table 7. mFOLFOX6 Dose Reductions - Non-neurological Toxicity

	Starting Dose (mg/m^2)	Dose Level – 1 (mg/m^2)	Dose Level- 2 (mg/m^2)
Oxaliplatin	85	65	50
5-FU Bolus	400	320	260
5-FU infusion	2,400	1,900	1,500

Table 8 describes the recommended dose modifications at the start of each subsequent course of therapy. All dose modifications should be based on the worst preceding toxicity. The dose of LV will not be adjusted due to toxicity. It should remain at 400 mg/m² racemate (or 200 mg/m^2 l-LV) for all courses. LV will be given immediately prior to each 5-FU dose; thus, if 5-FU is delayed, LV will be delayed.

Table 8. mFOLFOX6 Dose Modification Guidelines

Toxicity NCI Grade[a] (Value)	Dose Level for Subsequent Cycles Based on Interval Toxicity[b]	At Time of Retreatment
No toxicity	Maintain dose level	Maintain dose level
Neutropenia (ANC)		
Grade 1 (ANC <LLN - 1.5 x 10^9/L)	Maintain dose level	If ANC < 1.0 x 10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity. If ANC < 1.0 x 10^9/L after 4 weeks, discontinue therapy.
Grade 2 (ANC <1.5 x 10^9/L - 1.0 x 10^9/L)	Maintain dose level	
Grade 3 (ANC <1.0 x 10^9/L - 0.5 x 10^9/L)	Decrease both 5-FU & OXAL 1 dose level[c]	
Grade 4 (ANC < 0.5 x 10^9/L)	Decrease both 5-FU & OXAL 1 dose level[c]	
Thrombocytopenia		
Grade 1 (PLT < LLN - 75.0 x 10^9/L)	Maintain dose level	If PLT < 75.0 x 10^9/L at start of cycle, hold and check weekly then treat based on interval toxicity. If PLT < 75.0 x 10^9/L after 4 weeks, discontinue therapy.
Grade 2 (PLT < 75.0 x 10^9/L - 50.0 x 10^9/L)	Maintain dose level	
Grade 3 (PLT < 50.0 x 10^9/L - 25.0 x 10^9/L)	Decrease both 5-FU & OXAL 1 dose level	
Grade 4 (PLT < 25.0 x 10^9/L)	Decrease both 5-FU & OXAL 1 dose level	
Neutropenic fever[c,d]		
ANC <1.0 x 10^9/L (ie Grade 3 or 4 neutropenia) fever ≥ 38.5°C	Decrease both 5-FU & OXAL 1 dose level	
Other hematologic toxicities	Dose modifications for leukopenia at the start of subsequent courses of therapy and at time of retreatment are also based on NCI toxicity criteria (CTC Version 3.0) and are the same as recommended for neutropenia above.	

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[a] National Cancer Institute Common Toxicity Criteria (CTC Version 3.0).
[b] Refers to initial dose used in previous course.
[c] At the investigator's discretion, G-CSF should be used, and considered for use in subsequent cycles, according to standard of care, the most recent version of the product label in the region in which it is approved, and all applicable guidelines. G-CSF should not be administered in the period between 24 hours before and 24 hours after the administration of cytotoxic chemotherapy. Given the short (≤ 14 day) interval between treatment cycles, pegylated G-CSF should not be used. At the investigator's discretion, in subsequent cycles, treatment with oxaliplatin and 5-FU may be resumed at the dose used prior to the hematological toxicity, if ANC levels have returned to ≥ 1.0 x 10^9/L, and if all other criteria are met.
[d] In case of febrile neutropenia (ie, ANC < 1.0 x 10^9/L with fever ≥ 38.5°C) or grade ≥ 2 infection at any time, G-CSF should be used according to all applicable guidelines.
[e] For mucositis/stomatitis decrease only 5-FU, not Oxaliplatin.
[f] Exceptions: alopecia, fatigue, anorexia, nausea/vomiting (if can be controlled by antiemetics), viral infections.

Table 8. mFOLFOX6 Dose Modification Guidelines

Toxicity NCI Grade[a] (Value)	Dose Level for Subsequent Cycles Based on Interval Toxicity[b]	At Time of Retreatment
Diarrhea		
Grade 1	Maintain dose level	If Grade 2 diarrhea at start of cycle, hold and check weekly then treat based on interval toxicity.
Grade 2	Maintain dose level	
Grade 3	Decrease both 5-FU & OXAL 1 dose level	If Grade 2 diarrhea after 4 weeks, discontinue therapy.
Grade 4	Decrease both 5-FU & OXAL 1 dose level	
Other nonhematologic toxicities[e,f]	Dose modifications for other nonhematologic toxicities at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI toxicity criteria (CTC version 3.0) and are the same as recommended for diarrhea above.	
The dose of LV will not be adjusted due to toxicity. It should remain at 400 mg/m² racemate (or 200 mg/m^2 l-LV) for all courses. LV will be given immediately prior to each 5-FU dose; thus, if 5-FU is delayed, LV will be delayed.		

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[a] National Cancer Institute Common Toxicity Criteria (CTC Version 3.0).
[b] Refers to initial dose used in previous course.
[c] At the investigator's discretion, G-CSF should be used, and considered for use in subsequent cycles, according to standard of care, the most recent version of the product label in the region in which it is approved, and all applicable guidelines. G-CSF should not be administered in the period between 24 hours before and 24 hours after the administration of cytotoxic chemotherapy. Given the short (≤ 14 day) interval between treatment cycles, pegylated G-CSF should not be used. At the investigator's discretion, in subsequent cycles, treatment with oxaliplatin and 5-FU may be resumed at the dose used prior to the hematological toxicity, if ANC levels have returned to ≥ 1.0 x 10^9/L, and if all other criteria are met.
[d] In case of febrile neutropenia (ie, ANC < 1.0 x 10^9/L with fever ≥ 38.5°C) or grade ≥ 2 infection at any time, G-CSF should be used according to all applicable guidelines.
[e] For mucositis/stomatitis decrease only 5-FU, not Oxaliplatin.
[f] Exceptions: alopecia, fatigue, anorexia, nausea/vomiting (if can be controlled by antiemetics), viral infections.

Table 9 describes the recommended dose modifications of oxaliplatin based on the duration of oxaliplatin-associated neurotoxicity.

Table 9. Dose Modification Guidelines Oxaliplatin-associated Neurotoxicity

Toxicity (Grade)	Duration of Toxicity		Persistent (Not Resolved Between Cycles)
	1 - 7 Days	> 7 and < 14 Days	
Paresthesias/dysesthesias[a] of short duration that resolve and do not interfere with function (Grade 1)	No Change	No Change	No Change
Paresthesias/dysesthesias[a] interfering with function, but not activities of daily living (ADL) (Grade 2)	No Change	No Change	Decrease to 65 mg/m^2 or Hold until toxicity is < Grade 2
Paresthesias/dysesthesias[a] with pain or with functional impairment that also interfere with ADL (Grade 3)	1st time: Decrease to 65 mg/m^2 2nd time: Decrease to 40 mg/m^2	STOP	STOP
Persistent paresthesias /dysesthesias that are disabling or life-threatening (Grade 4)	STOP	STOP	STOP
Pharyngo-laryngeal dysesthesias	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours

[a] May be cold-induced

Subjects who discontinue oxaliplatin due to associated neurotoxicity should continue all other first-line treatment components of the regimen (5-FU/leucovorin, bevacizumab, and conatumumab). This modified first-line therapy will continue until one of the following occurs: disease progression, unacceptable adverse events, death, or the withdrawal of consent by the subjects.

6.3.3 Discontinuation of mFOLFOX6

Oxaliplatin and 5-FU/leucovorin will be administered until subjects develop disease progression, intolerability to each component, or withdrawal of consent.

Reintroducing mFOLFOX6 after permanent discontinuation will not be allowed as part of the first line treatment aspects of this trial.

6.3.4 Supportive Therapy for mFOLFOX6 Chemotherapy

6.3.4.1 Growth Factors

For low white blood cell counts, granulocyte-colony-stimulating factor (G-CSF) should be used in subjects with serious neutropenic complications such as febrile neutropenia, tissue infections, sepsis syndrome, fungal infection, etc. G-CSF should be used and

administered according to the product label or applicable guidelines. G-CSF should not be administered in the period between 24 hours before and 24 hours after the administration of cytotoxic chemotherapy. Given the short (≤ 14 day) interval between treatment cycles, pegylated G-CSF is not recommended.

For chemotherapy-induced anemia, erythropoiesis stimulating agents should be used and administered according to the product label or applicable guidelines.

6.3.4.2 Oral Cryotherapy

Subjects receiving oxaliplatin should not receive oral cryotherapy (ie. ice for mucositis prophylaxis) on Day 1 of each treatment cycle as this may exacerbate laryngopharyngeal dysesthesia caused by oxaliplatin.

6.3.4.3 Hypersensitivity

Platinum hypersensitivity can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment may include supplemental oxygen, standard epinephrine, corticosteroid, antihistamine therapy, bronchodilators or vasopressors. Platinum hypersensitivity is a rare event and should be treated promptly.

6.3.4.4 Pharyngolaryngeal Dysesthesias

Oxaliplatin may cause discomfort in the larynx or pharynx associated with dyspnea, anxiety and difficulty swallowing. This discomfort is exacerbated by cold. Appropriate therapy may include the use of antihistamine therapy, bronchodilators, cold avoidance or monitoring.

6.4 Bevacizumab (Transferring From Parent Protocol 20060464)

Please see package insert of bevacizumab for the most current storage and preparation instructions.

6.4.1 Bevacizumab Dosage, Administration and Schedule

Bevacizumab must be prepared by a healthcare professional using aseptic technique according to the most current label.

Bevacizumab will be administered at a dose of 5 mg/kg by intravenous infusion on day 1 of each 14 day cycle (+ 3 days). Institutional standards for bevacizumab infusion times may be used.

In the event that bevacizumab is discontinued for any reason prior to disease progression, mFOLFOX6 and conatumumab should continue on a once every 14 days (+ 3 days) schedule until disease progression or intolerance to the study therapy.

The highest dose tested in humans (20 mg/kg of body weight, IV) was associated with severe migraine in several subjects. Overdose with this product have not been reported.

If body weight changes exceed 10% of the baseline weight the bevacizumab dose will need to be re-calculated.

6.4.2 Bevacizumab Premedication

Any pre-medication for bevacizumab should be administered at the investigator's discretion and must be recorded in the appropriate electronic case report form.

6.4.3 Bevacizumab Toxicity Management

General toxicities associated with bevacizumab therapy (Avastin labeling text, 2009) include bleeding, arterial clots (which could lead to stroke and heart attack), bowel perforation, wound healing difficulties, and hypertension. Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation and in some instances with fatal outcome, occurs at an increased incidence in subjects receiving bevacizumab.

If bevacizumab is held due to toxicities, mFOLFOX6 and conatumumab should continue as planned and bevacizumab will be restarted at the next cycle of chemotherapy, so long as the toxicities have reduced in accordance with the protocol guidelines. Subjects will then resume bevacizumab treatment at the same dose and schedule.

See Table 10 for management of bevacizumab related toxicities.

For any subject experiencing grade 3 or 4 toxicity that persists for > 6 weeks or recurs after a dose delay, bevacizumab will be discontinued permanently.

6.4.4 Bevacizumab Dosage Adjustment

Reintroducing bevacizumab therapy after permanent discontinuation will not be allowed as part of the first-line treatment aspects of this trial. Bevacizumab should not be initiated for at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of bevacizumab. The half life of bevacizumab is estimated to be 20 days. Treatment should be suspended prior to elective surgery.

6.4.5 Discontinuation of Components of mFOLFOX6/Bevacizumab

Subjects who have intolerance to single or multiple components of the first-line treatment regimen (eg, oxaliplatin due to neurotoxicity), should continue all other first-line treatment components of the regimen (eg, 5-FU/leucovorin, bevacizumab, and conatumumab) on a once every 14 days (+ 3 days) schedule. This modified first-line therapy will continue until one of the following occurs: disease progression, unacceptable adverse events, death, or the withdrawal of consent by the subjects.

Table 10. Bevacizumab Treatment Delays and Instructions

Adverse Event	Grade CTCAE v3.0	Action to be Taken
Acute infusion reaction eg, fever, chills, headache, nausea (see Syndrome-Cytokine reaction, see CTCAE v 3.0 Appendix B) or Allergic reaction/hyper-sensitivity (eg, fever, rash, urticaria, bronchospasm)	1, 2 or 3	If infusion-related or allergic reactions occur, pre-meds should be given with the next dose and the infusion time should be increased by 30 minutes. If infusion-related AEs occur with the 30-min infusion, all subsequent doses should be given over 60 ± 10 min (with pre-meds). If infusion-related AEs occur with the 60-min infusion, all subsequent doses should be given over 90 ± 15 min (with pre-meds). For subjects with grade 3 reactions, the bevacizumab infusion should be stopped and not restarted on that day. At the physician's discretion, bevacizumab may be permanently discontinued or re-instituted with pre-medications and at a rate of 90 ± 15 min. If the reaction occurred at the 90-min rate, initially challenge at a slower infusion rate and gradually increase to 90 minutes. When bevacizumab is re-instituted, the subject should be monitored, per physician's usual practice, for a duration comparable to duration of reaction.
	4	Permanently discontinue bevacizumab.
Hemorrhage [a]	3 or 4	Permanently discontinue bevacizumab.
Thrombosis/thrombus/ embolism-venous (including vascular access device)	2 or 3	Hold bevacizumab until resolution by clinical assessment or Doppler. If the planned duration of full-dose anticoagulation is < 2 weeks, hold bevacizumab until anticoagulation is complete. If the planned duration of full-dose anticoagulation is ≥ 2 weeks, bevacizumab may be resumed during anticoagulation if no grade 3 or 4 hemorrhage event occurred while on therapy and: If stable dose of warfarin (or other anticoagulant), INR must be in range (usually between 2 and 3); or If unfractionated heparin, PTT must be in therapeutic range. Discontinue bevacizumab if thromboembolic events worsen or recur after resuming therapy.
	4	Permanently discontinue bevacizumab.
Visceral or peripheral arterial ischemia	2[b,c], 3 or 4	Permanently discontinue bevacizumab.
Cardiac ischemia/infarction	2[b], 3 or 4	Permanently discontinue bevacizumab.

[a] If coagulation disorders develop secondary to other medical conditions, hold bevacizumab until the INR and PTT return to ≤ grade 1.
[b] New or worsening grade 2 events. (Therapy may be continued for grade 2 conditions present at baseline that have not worsened.)
[c] Subjects who develop brief, reversible, exercise-induced claudication (grade 2) not attributable to arterial thromboembolic events may continue on study.
[d] Refer to grading criteria listed for the appropriate adverse event in the Infection Section of the CTCAE v 3.0.
[e] Refer to Dermatology/Skin Section of the CTCAE v 3.0.
[f] Determination of "clinically significant" is at the physician's discretion and applies to those adverse events that can be attributed to bevacizumab and are not related to chemotherapy.

Table 10. Bevacizumab Treatment Delays and Instructions

Adverse Event	Grade CTCAE v3.0	Action to be Taken
CNS ischemia	2[b], 3 or 4	Permanently discontinue bevacizumab.
GI perforation including GI leak and GI fistula	≥ 1	Permanently discontinue bevacizumab.
Intra-abdominal abscess [d]	3	Hold bevacizumab until resolved.
	4	Permanently discontinue bevacizumab.
Complication, non-infectious-wound dehiscence [e]	1	Hold bevacizumab for at least 1 month. If, in the physician's opinion, substantial healing has taken place within 1-3 months, bevacizumab may be resumed. If wound dehiscence recurs, permanently discontinue bevacizumab.
	2, 3, or 4	Permanently discontinue bevacizumab.
Proteinuria	2 (only if > 2 g/24 hrs) or 3	Hold bevacizumab until proteinuria improves to < 2 g of protein in a 24-hour urine collection. Re-check 24-hour urine protein every 2-4 weeks. If proteinuria does not improve to < 2 g/24 hrs within 3 months, permanently discontinue bevacizumab.
	4	Permanently discontinue bevacizumab.
Hypertension	3	Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician discretion. Bevacizumab should be held for uncontrolled or symptomatic hypertension present on the day that the bevacizumab dose is to be given. If BP is not controlled with medication within 1 month, permanently discontinue bevacizumab.
	4	Permanently discontinue bevacizumab.
Other clinically significant (AEs)[f]	3	Hold until AE has resolved to grade ≤ 1.
	4	Permanently discontinue bevacizumab.

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[a] If coagulation disorders develop secondary to other medical conditions, hold bevacizumab until the INR and PTT return to ≤ grade 1.
[b] New or worsening grade 2 events. (Therapy may be continued for grade 2 conditions present at baseline that have not worsened.)
[c] Subjects who develop brief, reversible, exercise-induced claudication (grade 2) not attributable to arterial thromboembolic events may continue on study.
[d] Refer to grading criteria listed for the appropriate adverse event in the Infection Section of the CTCAE v 3.0.
[e] Refer to Dermatology/Skin Section of the CTCAE v 3.0.
[f] Determination of "clinically significant" is at the physician's discretion and applies to those adverse events that can be attributed to bevacizumab and are not related to chemotherapy.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medication or treatment deemed necessary to provide adequate supportive care except for those listed above.

All prescribed and non-prescription concomitant medications that are administered, ingested, applied, or injected on an ongoing basis from the start of study treatment (or planned start of treatment in the case of subjects who have their first treatment delayed for any reason), as well as changes in such concomitant medication, and any new concomitant medication taken while the subject is on study should be recorded on the appropriate eCRF. Concomitant medications should be recorded until the Day 30 Safety Follow-up Visit or until 30 days after the last dose of protocol-specified treatment, whichever is later. Concomitant medications for medically significant adverse events, which are ongoing at the end of study treatment and considered related to study treatment, should be followed until the adverse event is resolved or considered stable.

6.6 Excluded Medications or Procedures During Study Period

The following therapies and treatments should not be administered while receiving protocol specified therapy during the study:

- Any investigational agent or other anti-tumor treatment (both standard and investigational)
- Chemotherapy, radiation therapy (except palliative radiation), hormone directed cancer therapy, or tumor directed antibody therapy other then therapy specified in this protocol
- Concurrent use of herbal medications or treatments
- Elective major surgeries during the study through 30 days after the last dose of protocol specified therapy. Subjects that undergo any unexpected major surgery during the course of the study must discontinue study treatment immediately and the study site should in turn notify the sponsor as soon as possible. Such cases will be reviewed by the Sponsor to determine whether the subject will be allowed to resume study treatment.

6.7 Metastases Interventional Therapy

Subjects that undergo interventional therapy for metastases (eg, surgical resection, radiofrequency ablation or cryotherapy) during the course of the study will do so according to standard institutional practice. Study treatment should be discontinued and the study site should in turn notify the sponsor as soon as possible. Such cases will be reviewed by the Sponsor to determine whether the subject will be allowed to resume study treatment.

6.8 Multiple Toxicity

If multiple or overlapping toxicity occurs, the most stringent dose modification criteria should be followed.

7. STUDY PROCEDURES

7.1 General Study Procedures

Refer to the Schedule of Assessments (see Appendix A) for an outline of procedures required at each visit. Blood samples for hematology, chemistry, and coagulation should be collected and submitted to the accredited local laboratory on the day of collection. Blood samples for antibody analyses should be shipped to Amgen (see Laboratory Manual and Appendix A).

Blood for antibody samples will be collected according to the schedule described in Sections 7.3 to 7.5 and Appendix A.

A summary of analytes to be tested in the study is provided in Table 11.

Table 11. Summary of Analytes Measured at Baseline / During the Study

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PTT	Specific gravity	RBC	Pregnancy Test
Potassium	INR	pH	Hemoglobin	Anti-conatumumab antibodies
Chloride		Blood	Platelets	Anti-AMG 479 antibodies
Albumin		Protein	WBC	HgbA1c*
Calcium		Glucose	ANC	
Magnesium			Differentials	
Phosphorus			• Neutrophils	
Glucose			• Lymphocytes	
BUN			• Monocytes	
Creatinine			• Eosinophils	
Uric acid			• Basophils	
Creatine Kinase				
Total bilirubin				
Alk phosphatase				
AST (SGOT)				
ALT (SGPT)				
Amylase				
Lipase				

* HgbA1c required for subjects with diabetes (Type 1 or Type 2) receiving AMG 479

7.2 Eligibility Assessment for Continued Treatment

Subjects must have their eligibility assessed for this study and be enrolled within 30 days of their last treatment on the parent protocol. Subjects will not be given the opportunity to be reassessed for eligibility should criteria not initially be met.

The eligibility assessment begins when the subject signs the IEC/IRB approved informed consent form and continues until study enrollment. A signed and dated IEC/IRB

informed consent (see Section 5) must be obtained before any specific procedures are performed. Only eligible subjects will be enrolled into this study.

The following eligibility assessments must be performed prior to enrollment:

- Review of inclusion/exclusion criteria
- Review of concomitant medications
- Review of medical history
- Physical exam including height
- Vital signs: resting pulse, respiration and temperature measurements, resting blood pressure (after subject has been seated for at least 5 minutes)
- Serum or urine pregnancy tests for female subjects of childbearing potential (within 3 days before enrollment)

If for any reason, the subject is not able to continue their treatment according to schedule, Amgen Sponsor approval should be obtained.

7.3 Treatment Period

Study day 1 is defined as the first day that protocol specific treatments begin. A cycle is defined as either 14 (+3) or 21 (± 3) days for conatumumab or 21 (± 3) days or 28 (± 3) days for AMG 479, respectively, (plus time to recover from toxicity if required), as per parent protocol. If Investigator decides to change the cycle duration from 2 to 3 weeks (for conatumumab) or 3 to 4 weeks (for AMG 479 if administered alone**)**, this must be decided prior to first dose and documented on the eCRF. The new cycle duration should remain the same throughout the duration of the protocol (allowing for time to recover from toxicity as required).

The following procedures will be performed up to 3 days before each investigational product(s) infusion unless otherwise indicated (Note: If baseline physical exam, vital signs, weight, and laboratory tests are performed within 7 days of Cycle 1 they do not need to be repeated at Cycle 1):

- Recording of concomitant medications, including those continuing from the parent protocol
- Recording all non-serious and serious adverse events beginning at the start of study treatment (or planned start of treatment in the case of subjects who have their first treatment delayed for any reason), including those continuing from the parent protocol
- All serious adverse events must be reported to Amgen within 24 hours following the investigator's knowledge of the event (see Section 9.2.2)
- Vital signs (resting pulse, respiration and temperature measurements, resting blood pressure [after subject has been seated for at least 5 minutes]) and weight

- Collection of samples for local laboratory assessment (see Table 11):
  - Hematology panel with 5 part differential
  - Comprehensive chemistry panel including sodium, potassium, chloride, albumin, calcium, magnesium, phosphorus, glucose, BUN, creatinine, creatine kinase, uric acid, total bilirubin, alkaline phosphatase, AST, ALT
  - Amylase and lipase
  - Urinalysis consisting of specific gravity, pH, blood, protein and glucose
  - Coagulation: PTT and INR
  - For subjects with diabetes (Type 1 or Type 2) who are receiving AMG 479, sample for HgbA1c collected at Cycle 1 and Cycle 3, and every 3 cycles thereafter (ie, C6, C9, etc).
- Collection of antibody samples, prior to infusion, for shipment to Amgen (refer to laboratory manual for detailed instructions):
  - Blood for anti-conatumumab antibody analyses collected every 8 cycles
  - For subjects receiving AMG 479 alone or in addition to conatumumab, blood for anti-AMG 479 antibody analyses collected every 8 cycles
- Infusion of investigational product(s) on Day 1 of each cycle;
  - For subjects receiving conatumumab refer to Section 6.1.1 for specifics on Dosage, Administration and Schedule
  - For subjects receiving infusion of AMG 479 alone or in addition to conatumumab, refer to Section 6.2.1 for specifics on dosage, administration and schedule
  - For subjects receiving FOLFOX6 plus bevacizumab in addition to conatumumab, refer to Sections 6.3.1 and 6.4.1 for specifics on dosage, administration and schedule
- Radiological assessments to evaluate disease extent (with change compared to nadir from the parent protocol) should be performed at regular intervals, at a minimum once every 6 (± 1) months or more frequently if clinically indicated (starting from their last scan on the parent protocol), per standard of care (SOC) at each facility

7.4 Day 30 Safety Follow-up Visit

Upon discontinuation of protocol-specified therapy, subjects will undergo the Safety Follow-up Visit assessment approximately 30 (+ 3) days after the last administration of conatumumab or AMG 479 if administered alone. NOTE: For subjects also receiving AMG 479 in combination with conatumumab, this visit occurs once both conatumumab and AMG 479 have been discontinued (see Section 6.2.3.1).

The following procedures will be performed:

- Recording of concomitant medications
- Review and recording of adverse events (see Section 9.1.2)

- Reporting of all serious adverse events to Amgen within 24 hours following the investigator's knowledge of the event (see Section 9.2.2)
- Clinical evaluation, including physical exam
- Vital signs: including pulse, respiration rate, temperature and blood pressure and weight
- Blood sample collection for local laboratory assessments (refer to Table 11 for analyte descriptions)
  - Hematology panel with differentials
- Comprehensive chemistry panel including sodium, potassium, chloride, albumin, calcium, magnesium, phosphorus, glucose, BUN, creatinine, creatine kinase, uric acid, total bilirubin, alkaline phosphatase, AST, ALT
  - Amylase and lipase
  - Coagulation: PTT and INR
  - Urinalysis consisting of specific gravity, pH, blood, protein and glucose
  - For subjects with diabetes who are receiving AMG 479, collect blood sample for HgbA1c
  - Serum or urine pregnancy tests for female subjects of childbearing potential
- Additional blood collection for anti-conatumumab antibody analyses and/or, blood collection for anti-AMG 479 antibody analyses

7.5 Day 60 Follow-up Visit

Obtain serum samples for anti-conatumumab antibody analyses and/or anti-AMG 479 antibody analyses, at 60 (± 14) days after the date of the last administration of protocol-specified therapy, unless the subject has started another systemic anti-cancer therapy.

NOTE: If a subject tests positive for the development of anti-conatumumab or anti-AMG 479 neutralizing antibodies, serum samples will be taken every 12 (± 2) weeks from the time the site is notified by Amgen that a subject tested positive for neutralizing antibodies until antibody levels return to baseline (or become negative), start of new anti-cancer therapy, or up to 1 year from the last dose of protocol-specified therapy, whichever occurs first.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Subjects have the right to withdraw fully from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Withdrawal of full consent for this study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further

study participation; subject data up to withdrawal of consent will be included in the subject's study data. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study.

There will be no partial consent withdrawal in this study.

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable CRFs.

Reasons for removal from protocol-specified product(s) or observation might include:

- withdrawal of full consent
- administrative decision by the investigator or Amgen
- pregnancy in a female subject (report on Pregnancy Notification Worksheet; see Appendix D)
- pregnancy in female partner of a male subject if he is unwilling to use a condom during treatment and for 6 months after the end of treatment (report pregnancy on Pregnancy Notification Worksheet; see Appendix D)
- ineligibility
- significant protocol deviation
- subject noncompliance
- adverse event
- disease progression
- requirement for alternative therapy
- protocol-specified criteria
- other safety concern by the investigator or Amgen
- death

8.2 Replacement of Subjects

There will be no replacement of subjects.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.

The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

Disease progression of the primary tumor itself is not considered an adverse event; however, signs and symptoms of disease progression may be recorded as adverse events or serious adverse events. If a new primary tumor malignancy appears, it will be considered an adverse event.

Deaths due to progressive disease during treatment until the Safety Follow-up Visit or 30 days after the last dose of protocol specified therapy, whichever is later, should be recorded as due to the primary tumor.

Interventions for pretreatment conditions (eg, elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered adverse events.

9.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined in Section 9.1 and as further specified below) observed by the investigator or reported by the subject that occur after the start of study treatment (or planned start of treatment in the case of subjects who have their first treatment delayed for any reason) through the Safety Follow-up Visit or 30 days post the last dose of protocol-specified therapy are collected and reported using the applicable CRF (eg, Adverse Event Summary CRF). In addition, adverse events that were continuing at the end of the parent study must be recorded and followed through to the stop date or the Safety Follow-up Visit. Adverse events should also be collected and recorded in the subject's medical records and serious adverse events should be recorded on the Serious Adverse Event Report (SAER) form. These adverse events will include the following:

- All serious adverse events (as defined in Section 9.2.1) that occur after the start of study treatment (or planned start of treatment in the case of subjects who have their first treatment delayed for any reason) through to the Safety Follow-up Visit or 30 days after the last dose of protocol-specified therapy, whichever is later.

- All non-serious adverse events (as defined in Section 9.1.1) beginning at the start of study treatment (or planned start of treatment in the case of subjects who have their first treatment delayed for any reason) through to the Safety Follow-up Visit or 30 days after the last dose of protocol-specified therapy, whichever is later.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution,
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to conatumumab (and/or AMG 479 if applicable), and
- Action taken.

The adverse event severity grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The severity grading scale used in this study is described in Appendix B.

The investigator must assess whether the adverse event is possibly related to the investigational product(s) and/or other study drugs. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s) and/or other study drugs?

The investigator must assess whether the adverse event is possibly related to any study-mandated procedure or activity. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study procedure/activity"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) should be recorded as the adverse event.

The investigator's clinical judgment will be used to determine whether a subject should be removed from treatment or from the study due to an adverse event. A subject, or subject's parent/legal guardian, may also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws full consent, the subject should be encouraged to undergo, at a minimum, the Safety Follow-up Visit.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal,
- life threatening (places the subject at immediate risk of death),
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- congenital anomaly/birth defect, and/or
- other medically important serious event.

An adverse event would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of “other medically important serious event”. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

Since the criteria for CTCAE severity differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 “life threatening” CTCAE severity criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator’s judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event’s severity status must be recorded in the subject’s medical record.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur from the start of study treatment (or planned start of treatment in the case of subjects who have their first treatment delayed for any reason) through to the Safety Follow-up Visit or 30 days after the last dose of protocol-specified therapy, whichever is later, are recorded in the subject’s medical record and are reported to Amgen via a Serious Adverse Event Report (SAER) form. The SAER must be submitted to Amgen within 24 hours of following the investigator’s knowledge of the event. See Appendix C for a sample of the SAER form.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

New information relating to a previously (while subject was treated on the parent study) reported serious adverse event must be recorded on an SAER form using the subject's ID and protocol number from the parent study. New serious adverse events occurring after the start of study 20101116 treatment (or planned start of treatment in the case of subjects who have their first treatment delayed for any reason) must be recorded on an SAER using the subject's ID and protocol number from this study. All changes to SAER forms must be sent to Amgen within 24 hours following the investigator's knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided on the SAER form must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

Hospitalization for events requiring anticipated protocol-specified procedures, such as hospitalization for administration of chemotherapy or central line insertion and elective hospitalizations are not considered serious adverse events. However, if an adverse event occurs during the hospital visit for one of these procedures and meets the definition of serious, then it must be reported as a serious adverse event.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen and included on the Serious Adverse Event Report Form as well as the appropriate CRF.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions (SUSARs) as required to regulatory authorities, investigators/institutions, and IRBs/ECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator should notify the appropriate IRB/EC/head of the medical institution of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.3 Pregnancy and Lactation Reporting

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 6 months after the end of treatment.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation.

Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- **Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 6 months after the end of treatment.**
- **Information will be recorded on the Pregnancy Notification Worksheet (Appendix D). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)**
- **After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 6 months after the end of treatment of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).**
- **Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.**
- **While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.**
- **If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a**

spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix C. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment.

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 6 months after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information. After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 6 months after the end of treatment.
- Information will be recorded on the Lactation Notification Worksheet (Appendix E) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 204 (see Section 4.2).
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant

health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 6 months after the end of treatment after discontinuing protocol-required therapies.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

The endpoints for this study include:

- Adverse events
- Serious adverse events
- Vital signs
- Clinical laboratory tests
- Tumor response
- Disease progressions and deaths

10.2 Sample Size Considerations

The sample size for this study cannot be determined prospectively, as it is contingent on the number of subjects still receiving conatumumab or AMG 479 on the parent studies. The sample size is estimated to be approximately 15 subjects.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

This is an open-label study. All study team members, investigators, and subjects will have access to study treatment information.

10.4 Planned Methods of Analysis

10.4.1 General Approach/Considerations

The studies preceding this open label extension are sufficiently different to preclude pooling over the studies. Since the number of subjects enrolled per parent study will be low most of the data will be shown in listings. A limited number of summary tables will be produced when the number of subjects makes this sensible.

The final analysis of this study will be performed at the end of the study ie, when all the subjects have completed or had the opportunity to complete the Day 60 Follow-up visit. The data may be summarized and listed before the final analysis to support Regulatory filings.

Subject disposition (number screened, enrolled into the study, receive conatumumab and/or AMG 479, withdraw from the study) will be summarized.

Demographics (age, sex, race) and tumor type will be listed.

10.4.2 Analysis of Key Study Endpoints

10.4.2.1 Safety Endpoints

Analyses of safety will be carried out for all subjects who enrolled into this study.

All reported adverse events will be assigned to a system organ class and preferred term within a system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 or later. The adverse events (all, serious, and related) will be listed by subject, system organ class, preferred term, and severity. Further listings will show events that were continuing at the end of the parent study, on-study deaths, serious and significant adverse events, including early withdrawals due to adverse events.

Adverse events will be reported up to 30 days after last dose of investigational product.

Listings will be provided for hematology, chemistry, and urinalysis parameters, as well as for vital sign variables. Listings will be provided for baseline pre-study measurements, minimum observed on-study measurement, maximum observed on-study measurement and last observed measurement (including change from baseline to each).

10.4.2.2 Tumor Response, Disease Progression and Deaths

Analyses of tumor response, disease progression and deaths will be carried out for all subjects who enrolled into this study.

Listings will be provided for tumor response, disease progression, and deaths.

Overall survival is the time, in months, from randomization into the parent study to the day of death. Subjects who have not died while on the study or are lost to follow-up will be censored at the date of last contact. Subjects who withdraw consent will be censored on the date of withdrawal.

Progression-free survival is the time, in months, from randomization/enrollment into the parent study to the first observation of disease progression or death due to any cause. For the progression-free survival analysis the following censoring strategies for missing dates of disease progression will be used:

- If a subject's disease has not progressed and the subject is alive, progression-free survival will be censored at the last date they are known to be progression-free (ie, the last tumor evaluation date).
- If a subject has no tumor evaluation in either the parent study or the extension study, progression-free survival will be censored at the date of randomization into the parent study.

- Subjects who withdraw consent to participate in the study prior to progression will be censored at their last evaluable tumor assessment**.**

If sufficient subjects enrolled from parent studies then Kaplan-Meier plots of progression free survival and overall survival will be shown for each parent study.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the Amgen study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the

subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product(s).

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB/head of the medical institution of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IEC/IRB continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- On the eCRFs or other documents submitted to Amgen, subjects should be identified by a subject identification number only, with a complete and accurate date of birth on the demographics eCRF.
- On Serious Adverse Event forms submitted to Amgen, subjects should be identified by their initials and a subject identification number only.
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records, including personal information, without violating the confidentiality of the subject.

11.4 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of Amgen. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval. The investigator/institution must send a copy of the approval letter from the IEC/IRB to Amgen.

Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study. Amgen reserves the right to terminate the study. The investigator should notify the IEC/IRB/head of the medical institution in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12.2 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed eCRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the IEC/IRB and Amgen
- If kept, proof of receipt/delivery sheet, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs (eCRFs) must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".

- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the investigator inspected or reviewed the data on the CRF and the data queries, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Appendix A), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country-specific requirements for language requirements.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal investigators and appropriate

Amgen staff. The committee is expected to solicit input and assistance from other investigators and Amgen staff as appropriate. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship—the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Study Agreement among the institution, principal investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Subject will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent Template. Depending on the type of study, subjects may be compensated for other inconveniences not associated with study-related injuries (eg, travel costs).

13. REFERENCES

Avastin® (Bevacizumab) Final Labeling Text, U.S. BL 125085/168 Amendment: Bevacizumab-Genentech, Inc. July 2009.

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Sachdev D, Yee D. Disrupting insulin-like growth factor signaling as a potential cancer therapy. *Mol Cancer Ther.* 2007;6:1-12.

Werner H, LeRoith D. The role of the insulin-like growth factor system in human cancer. *Adv Cancer Res*. 1996;68:183-223.

14. APPENDICES

Appendix A. Schedule of Assessments

	Eligibility Assessments	Treatment Period								Follow-up Period	
Cycles (Q2W, Q3W, or Q4W)		1	2	3	4	5	6	7	≥8	Day 30 Safety Follow-up	Day 60 Follow-up
Days		1	1	1	1	1	1	1	1	30 days	60 days
GENERAL & SAFETY ASSESSMENTS											
Informed consent	X										
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	
Physical exam	X									X	
Vital signs	X	X	X	X	X	X	X	X	X	X	
Weight		X	X	X	X	X	X	X	X	X	
Height	X										
LABORATORY ASSESSMENTS & CONATUMUMAB DOSING											
Pregnancy test	X[a]									X	
Coagulation (PTT, INR)		X	X	X	X	X	X	X	X	X	
Hematology		X	X	X	X	X	X	X	X	X	
Chemistry		X	X	X	X	X	X	X	X	X	
Serum amylase & lipase		X	X	X	X	X	X	X	X	X	
Urinalysis		X	X	X	X	X	X	X	X	X	
HgbA1c [b]		X		X			X (q3c)			X	
Anti-AMG 479 antibody[c]		q8c								X	X[e]
Anti-conatumumab antibody[d]		q8c								X	X[e]
Conatumumab infusion[f]		X	X	X	X	X	X	X	X		
CHEMOTHERAPY & OTHER BIOLOGICS DOSING											
AMG 479 infusion[g]		X	X	X	X	X	X	X	X		
Leucovorin, Oxaliplatin & 5-FU Bolus Infusion [h]		X	X	X	X	X	X	X	X		
Bevacizumab Infusion [i]		X	X	X	X	X	X	X	X		
5-FU 46-48 Hour Ambulatory Infusion[j]		X	X	X	X	X	X	X	X		
RADIOLOGICAL ASSESSMENTS											
Staging [k]		SOC									

Footnote defined on the next page

[a] Pregnancy test within 3 days before enrollment.
[b] HgbA1c will be collected for diabetic subjects who are receiving AMG 479 at cycle 1, cycle 3 and every 3 cycles thereafter (ie, C6, C9, etc).
[c] Anti-AMG 479 antibody will be collected at a frequency of every 8 cycles from study day 1 only for subjects receiving treatment with AMG 479 (subjects who were previously on the 20070411 or 20050118 Amgen protocol). A sample will also be collected at SFU and the Day 60 Follow-up visit, unless another anti-cancer therapy has started.
[d] Anti-conatumumab antibody will be collected at a frequency of every 8 cycles from study day 1. A sample will also be collected at SFU and the Day 60 Follow-up visit, unless another anti-cancer therapy has started.
[e] Day 60 Follow-up: If a subject tests positive for the development of anti-conatumumab or anti-AMG 479 neutralizing antibodies, serum samples will be taken every 12 (± 2) weeks from the time the site is notified by Amgen that a subject tested positive for neutralizing antibodies until antibody levels return to baseline (or become negative), start of new anti-cancer therapy, or up to 1 year from the last dose of protocol-specified therapy, whichever occurs first.
[f] Conatumumab will be administered on day 1 of each 14 (+ 3) or 21 (± 3) day cycle.
[g] AMG 479 will be administered on day 1 of each 21 (± 3) or 28 (± 3) day cycle.
[h] Leucovorin, Oxaliplatin & 5-FU Bolus infusion regimen is administered at every cycle (q2w schedule) for subjects with metastatic colorectal cancer who were previously receiving this treatment on the 20060464 Amgen protocol.
[i] Bevacizumab infusion regimen is administered at every cycle (q2w schedule) for subjects with metastatic colorectal cancer who were previously receiving this treatment on the 20060464 Amgen protocol.
[j] 5-FU 46-48 Hour Ambulatory Infusion regimen is administered at every cycle (q2w schedule) for subjects with metastatic colorectal cancer who were previously receiving this treatment on the 20060464 Amgen protocol.
[k] Radiological assessments to evaluate disease extent (with change compared to nadir from the parent protocol) should be performed at regular intervals, at a minimum once every 6 (± 1) months or more frequently if clinically indicated (starting from their last scan on the parent protocol), per standard of care (SOC) at each facility.

Appendix B. Additional Safety Assessment Information

Adverse Event Severity Scoring System

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

Drug-induced Liver Injury Assessment and Monitoring

Reporting: Regardless of attribution or etiology, in order to monitor for signals of protocol-specified therapy induced liver injury, the following events should be reported as Serious Adverse Events and recorded on the Adverse Events CRF.

Notify the Sponsor within 24 hours:

- AST or ALT ≥ 3 times the upper limit of normal AND with serum bilirubin ≥ 2 times the upper limit of normal of the reference laboratory
- Unexplained AST or ALT > 8 times the upper limit of normal
- AST or ALT ≥ 3 times the upper limit of normal with clinical signs or symptoms of hepatitis (eg, jaundice, right upper quadrant abdominal pain)

If the cause of the liver test abnormalities is apparent and not attributable to protocol-specified therapy, adjust dosing per dose modification guidelines in Section 6.

For sustained elevations, submit as additional information to the initial SAE report

For recurrent elevations:

- ≤ 30 days of the initial SAE report and have the same etiology, report as additional information to the original SAE.
- ≥ 30 days or different event, report as new SAE

If the cause of the liver test abnormalities is not known, manage as a potential drug-induced liver injury:

- Withhold protocol-specified therapy (see Section 6)

Evaluation: consider viral hepatitis A, B, or C, preexisting or acute liver disease, liver metastases, fatty liver, or another drug(s) capable of causing the observed injury.

- Perform clinical follow-up, including repeat liver enzymes (AST, ALT, total bilirubin, alkaline phosphatase, INR) within 48-72 hours
- Consider hepatitis serology, imaging, or other testing required to establish cause

- Obtain a more detailed history of:
  - symptoms (if applicable) including hypersensitivity type reactions, fatigue, nausea, vomiting, fever, or eosinophilia.
  - prior and/or concurrent conditions, including use of alcohol, drugs and special diets
  - concomitant medications (including non-prescription medicines, herbal and dietary supplements)
- Follow the subject until all abnormalities return to baseline or normal. Follow up should be for a minimum of 4 weeks after protocol-specified therapy discontinuation.

The potential drug-induced liver injury event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding eCRFs.

Appendix C. Sample Serious Adverse Event Form

The following minimum fields must be completed prior to faxing the form:
1) Site Number; 2) Subject ID Number; 3) Serious Adverse Event Diagnosis; Serious Criteria Code; Start Date of Event; 10) Signature
Ensure both pages are faxed with each submission.

Note: Only events that meet serious criteria should be reported on this form.

Submit a Serious Adverse Event Report (SAER) form within 24 hours of the Investigator's knowledge of the event.

Data on the AE Summary CRF must agree with data submitted on the SAER form in the following areas: adverse event term(s), serious criteria, and relationship of product to event.

Only include information that is relevant (pertinent) to the event(s) included on this SAER (eg, concomitant medications, medical history, laboratory and diagnostic tests)

Header Information

New / Follow-up – Indicate if this is a new adverse event, or a follow-up of a pre-reported event.

Follow-up – Send a follow-up report if additional data adds to or changes the clinical interpretation of the event. Some examples are:

- The initial reported event has changed and additional serious criteria have been met (such as if event outcome is now fatal).
- Signs and symptoms were reported at the time of the initial report and a final diagnosis has now been made.
- A change in relationship of a study procedure or activity has occurred from the initial report.
- A significant change has occurred in the start date of the event or start date of a suspect concomitant medication.
- Additional concomitant medications and/or diagnostics have been identified that may contribute to or explain the event.

When sending a follow-up report, either:

- On a photocopy of the prior report, add the additional information, re-sign and date, then fax in the follow-up form – or –
- Complete a new form with the new information. If the serious adverse event terms have not changed, please write, in section 3, the following: "No changes in serious adverse event terms from previous SAER form," then fax in the follow-up form.
- If a new serious adverse event term is to be added to the terms previously reported, add this new term to a photocopy of the initial form.
- If an earlier reported adverse event is being replaced by a new diagnosis or event term, on a photocopy of the initial report, strike through the term to be deleted, sign and date the deletion, and add the updated event term.

1. Site Information

Site Number – Enter your assigned site number for this study

Investigator, Country, Reporter, Phone No., and Fax No. – Enter information requested

2. Subject Information

Subject ID Number – Enter the entire number assigned to the subject

Date of Birth, Sex, and Race – Enter the subject's demographic information

3. Serious Adverse Event

Provide the date the Investigator became aware of this Serious Adverse Event Information

Serious Adverse Event Diagnosis or Syndrome –

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms meeting serious criteria should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available. Do not enter "Death", as this is an outcome, not an event.

Date Started – Enter date the adverse event first started, not when the event met serious criteria, when a diagnosis was made or when the subject was hospitalized.

Date Ended – Enter date the adverse event ended, not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

Serious Criteria Code – Enter reason why the reported event has met serious criteria:

- Immediately life-threatening **–** Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other significant medical hazard" may be the appropriate serious criteria.

Relationship to IP* – The Investigator must determine and enter the relationship of the event to the IP at the time the event is

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Instruction Page **1** of **2**

initially reported. **This is a mandatory field.**
Relationship to Amgen device – The Investigator must determine and enter the relationship of the event to the Amgen device at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field.**

Outcome of Event – Enter the code for the outcome of the event at the time the form is completed.
- Resolved – End date is known
- Resolving / Not resolved – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy, or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to concomitant administration – only diagnostic tests or activities mandated by the protocol.

4. Hospitalization

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study, which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt. However, if the subject is retained in the study unit and becomes an inpatient due to an AE, the event would be reportable as an SAE.

5. Investigational Product

Investigational Product – If applicable, indicate whether the Investigational Product is blinded or open-label

Initial Start Date – Enter date the product was first administered, regardless of dose.

Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event

6. Concomitant Medications

Indicate if there are any concomitant medications, including protocol-specified diluents and challenge agents.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is suspect for the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

7. Relevant Medical History

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. Relevant Laboratory Tests

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run, and the results.

9. Other Relevant Tests

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

10. Case Description

Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6).

Footer

Signature, Title, and Date – The Investigator or designee must sign the form and provide their title and date. Designee must be identified on the Delegation of Authority form.

AMGEN 20101116

Clinical Trial Serious Adverse Event Report – Phase 1–4

Notify Amgen Within 24 Hours of knowledge of the event

☐New ☐Follow-up

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day Month Year	Sex	Race
		☐F ☐M	

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____Month____Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by IP? If yes see section 10 No✓	 Yes✓	Relationship Is there a reasonable possibility that the event may have been caused by an Amgen device? No✓	 Yes✓	 If Yes, what device?	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure *eg, biopsy*

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product **01** Still being Administered **02** Permanently discontinued **03** Withheld
<<IMP>> ☐✓Blinded ☐✓Open Label						

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

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AMGEN 20101116	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Test / Unit									
	Test									
	Unit									

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date

Appendix D. Pregnancy Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20101116

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____ / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm_____ / dd_____ / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____ / yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____ / dd_____ / yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____ / dd_____ / yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011

Page 1 of 1

Appendix E. Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 2010116

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Amendment 5

Protocol Title:
A Phase 2 Open Label Extension Study of Conatumumab and AMG 479

Amgen Protocol Number AMG 655 (Conatumumab) and AMG 479 20101116

Amendment Date: 11 April 2017

Rationale:

- To describe the two-step transition to NantCell in manufacturing, labeling, and distribution of AMG 479.
- To update the Key Sponsor Contacts
- To update Section 9.3, Pregnancy and Lactation Reporting
- To update Appendix C, Sample Serious Adverse Event Form, Appendix D, Pregnancy Notification Worksheet, and Appendix E, Lactation Notification Worksheet

Description of Changes:

Section: Global

Replace:

20 November 2013

With:

11 April 2017

Section: Title Page

Key Sponsor Contact(s)

Replace:

[redacted], MD, PhD
Clinical Research Medical Director
Amgen Inc.
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

With:

[redacted], MD
Clinical Research Senior Medical Scientist
Amgen Inc.
Phone: [redacted]
E-mail: [redacted]

Replace:

[redacted]
Clinical Research Study Manager
Amgen Inc.
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

With:

[redacted]
Global Clinical Trial Manager
DOCS International UK Ltd
Phone: [redacted]
E-mail: [redacted]

Add:

Amendment 5: 11 April 2017

Section: 6.2 AMG 479

Add:

AMG 479 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study distribution procedures. **Upon the appropriate approvals being received, AMG 479 will be manufactured and packaged by Amgen, and labelled and distributed by NantCell using NantCell clinical study distribution procedures. Subsequent to this, and subject to the appropriate approvals being in place, AMG 479 will be manufactured, packaged, labelled, and distributed by NantCell, using NantCell clinical study distribution procedures.** Refer to the Investigational Product Instruction Manual for details regarding packaging, labeling, storage, and dispensing of AMG 479.

Section: 9.3 Pregnancy and Lactation Reporting

Replace:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified product and for 6 months after end of treatment, the pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 7 business days of the site receiving notification of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix D). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, Investigators should monitor for lactation cases that occur after the last dose of protocol-specified product through 6 months after of end of treatment.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 7 business days of the site receiving notification. Report a lactation case on the Lactation Notification Worksheet (Appendix E).

With:

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 6 months after the end of treatment.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation.

Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- **Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 6 months after the end of treatment.**
- **Information will be recorded on the Pregnancy Notification Worksheet (Appendix D). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)**
- **After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 6 months after the end of treatment of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).**
- **Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.**
- **While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.**
- **If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.**
- **Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described**

in Appendix C. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.

- **Any female subject who becomes pregnant while participating will discontinue study treatment.**

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- **In the event a male subject fathers a child during treatment, and for an additional 6 months after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)**
- **The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information. After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.**
- **Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).**
- **Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.**

Collection of Lactation Information

- **Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 6 months after the end of treatment.**
- **Information will be recorded on the Lactation Notification Worksheet (Appendix E) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.**
- **Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 204 (see Section 4.2).**

With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 6 months after the end of treatment after discontinuing protocol-required therapies.

Section: 14 - Appendices

Replace:

AMGEN 20101116	Clinical Trial Serious Adverse Event Report *Notify Amgen Within One Working Day*	☐New ☐Follow-up

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Initials	Date of Birth Day Month Year	Sex ☐F ☐M	Race

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event co-occurred before first dose of IP	Enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the event may have been caused by If yes see section 10				Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure e.g. biopsy
					AMG 555		AMG 479			
					No✓	Yes✓	No✓	Yes✓		

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

6. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld
AMG 555 ✓ Open Label						
AMG 479 ✓ Open Label						

8. RELEVANT CONCOMITANT MEDICATIONS (e.g. chemotherapy) Any Relevant Medications? No Yes, If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

FORM-015482 v3.0 Effective date: 08-Sep-2009 Page 1 of 2 *SAER Created:11-Aug-2010*

AMGEN 20101116	Clinical Trial Serious Adverse Event Report *Notify Amgen Within One Working Day*	❑New ❑Follow-up

Site Number	Subject ID Number

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and anyrelevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Test												
Date (Day Month Year)	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date

FORM-015482 v3.0 Effective date: 08-Sep-2009 Page 2 of 2 *SAER Created:11-Aug-2010*

With:

The following minimum fields must be completed prior to faxing the form:
1) Site Number; 2) Subject ID Number; 3) Serious Adverse Event Diagnosis; Serious Criteria Code; Start Date of Event; 10) Signature
Ensure both pages are faxed with each submission.

Note: Only events that meet serious criteria should be reported on this form.

Submit a Serious Adverse Event Report (SAER) form within 24 hours of the Investigator's knowledge of the event.

Data on the AE Summary CRF must agree with data submitted on the SAER form in the following areas: adverse event term(s), serious criteria, and relationship of product to event.

Only include information that is relevant (pertinent) to the event(s) included on this SAER (eg, concomitant medications, medical history, laboratory and diagnostic tests)

Header Information

New / Follow-up – Indicate if this is a new adverse event, or a follow-up of a pre-reported event.

Follow-up – Send a follow-up report if additional data adds to or changes the clinical interpretation of the event. Some examples are:

- The initial reported event has changed and additional serious criteria have been met (such as if event outcome is now fatal).
- Signs and symptoms were reported at the time of the initial report and a final diagnosis has now been made.
- A change in relationship of a study procedure or activity has occurred from the initial report.
- A significant change has occurred in the start date of the event or start date of a suspect concomitant medication.
- Additional concomitant medications and/or diagnostics have been identified that may contribute to or explain the event.

When sending a follow-up report, either:

- On a photocopy of the prior report, add the additional information, re-sign and date, then fax in the follow-up form – or –
- Complete a new form with the new information. If the serious adverse event terms have not changed, please write, in section 3, the following: "No changes in serious adverse event terms from previous SAER form," then fax in the follow-up form.
- If a new serious adverse event term is to be added to the terms previously reported, add this new term to a photocopy of the initial form.
- If an earlier reported adverse event is being replaced by a new diagnosis or event term, on a photocopy of the initial report, strike through the term to be deleted, sign and date the deletion, and add the updated event term.

1. Site Information

Site Number – Enter your assigned site number for this study

Investigator, Country, Reporter, Phone No., and Fax No. – Enter information requested

2. Subject Information

Subject ID Number – Enter the entire number assigned to the subject

Date of Birth, Sex, and Race – Enter the subject's demographic information

3. Serious Adverse Event

Provide the date the Investigator became aware of this Serious Adverse Event Information

Serious Adverse Event Diagnosis or Syndrome –

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms meeting serious criteria should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available. Do not enter "Death", as this is an outcome, not an event.

Date Started – Enter date the adverse event first started, not when the event met serious criteria, when a diagnosis was made or when the subject was hospitalized.

Date Ended – Enter date the adverse event ended, not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

Serious Criteria Code – Enter reason why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other significant medical hazard" may be the appropriate serious criteria.

Relationship to IP* – The Investigator must determine and enter the relationship of the event to the IP at the time the event is

initially reported. **This is a mandatory field.**
Relationship to Amgen device – The Investigator must determine and enter the relationship of the event to the Amgen device at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field.**

Outcome of Event – Enter the code for the outcome of the event at the time the form is completed.
- Resolved – End date is known
- Resolving / Not resolved – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy, or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to concomitant administration – only diagnostic tests or activities mandated by the protocol.

4. Hospitalization

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study, which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt. However, if the subject is retained in the study unit and becomes an inpatient due to an AE, the event would be reportable as an SAE.

5. Investigational Product

Investigational Product – If applicable, indicate whether the Investigational Product is blinded or open-label

Initial Start Date – Enter date the product was first administered, regardless of dose.

Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event

6. Concomitant Medications

Indicate if there are any concomitant medications, including protocol-specified diluents and challenge agents.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is suspect for the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

7. Relevant Medical History

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. Relevant Laboratory Tests

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run, and the results.

9. Other Relevant Tests

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

10. Case Description

Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6).

Footer

Signature, Title, and Date – The Investigator or designee must sign the form and provide their title and date. Designee must be identified on the Delegation of Authority form.

AMGEN 20101116	**Clinical Trial Serious Adverse Event Report – Phase 1–4** ***Notify Amgen Within 24 Hours of knowledge of the event***	❑New ❑Follow-up

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report (Day Month Year)

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth (Day Month Year)	Sex	Race
		☐F ☐M	

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day_____Month____Year_____

Serious Adverse Event Diagnosis or Syndrome **If diagnosis is unknown, enter Signs / Symptoms** **When Final Diagnosis is known, enter as Adverse Event** *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the event may have been caused by IP? **If yes see section 10** No✓	 Yes✓	**Relationship** Is there a reasonable possibility that the event may have been caused by an Amgen device? No✓	 Yes✓	 **If Yes, what device?**	**Outcome of Event** **01** Resolved **02** Resolving **03** Not resolved **04** Fatal	Check only if event is related to study procedure *eg, biopsy*

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted (Day Month Year)	Date Discharged (Day Month Year)
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product **01** Still being Administered **02** Permanently discontinued **03** Withheld
<<IMP>> ☐✓Blinded ☐✓Open Label						

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

AMGEN 20101116	**Clinical Trial Serious Adverse Event Report – Phase 1–4** ***Notify Amgen Within 24 Hours of knowledge of the event***	❑New ❑Follow-up

	Site Number	Subject ID Number	

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Test / Unit									
	Unit									

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date

Section: Appendix D. Pregnancy Notification Worksheet

Replace:

AMGEN™ Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A PAGE

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm ▼ / dd ▼ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm▼/dd▼/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ▼ /dd ▼ /yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ▼ / dd ▼ / yyyy____ ☐ Unknown

Estimated date of delivery mm ▼ / dd ▼ / yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ▼ / dd ▼ / yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ▼ / dd ▼ / yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

With:

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20101116

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____ / dd_____/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: March 27, 2011

Page **1** of **1**

Section: Appendix E. Lactation Notification Worksheet

Replace:

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

With:

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 2010116

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: 03 April 2012, version 2.

Page **1** of **1**

Amendment 4

Title: A Phase 2 Open Label Extension Study of Conatumumab and AMG 479

Amgen Protocol Number (Conatumumab and AMG 479) 20101116

Amendment Date: 20 November 2013

Rationale:

The protocol was amended primarily to change the interval of tumor scans from 3 to 6 months (±1 months or more frequently if clinically indicated) in order to reduce the risk to subjects due to potential cumulative radiation exposure given that all subjects have been on study treatment for 3.5 to 7 years since the initial dose on the Parent Study and continue to do well either responding to treatment or are clinically stable.

In the addition, the following changes have been incorporated into the protocol:

- Update the sponsor contact information.
- Remove the description of the formulation of the conatumumab and AMG 479 investigational product materials from the protocol since the information is already provided to the investigator in the Investigational Product Instruction Manual.
- Allow the investigator to use previous cycle's amylase and lipase results, if present cycle's results are not available before dosing
- Revision of the reporting language of SAE's within the Treatment period and Day 30 Safety Follow Up Visit (sections 7.3 and 7.4)
- Update reasons for removal from protocol-specified product(s) or observation in Section 8.1 in accordance with reasons available on the end of study case report form.
- Update Section 9.2.2 (Reporting Procedures for SAE) to inform the investigator to report SAEs that occurs outside the protocol-specified reporting period per the Guidance CT-3.
- Update EAC data capture instructions in Section 12.3 (Study Monitoring and Data Collection) to align with the current standard instructions in the Amgen protocol template.
- Add Section 12.4 (Investigator Responsibilities for Data Collection) per the latest version of the Amgen protocol template
- Update Section 12.6 (Publication Policy) to only reference the International Committee Medical Journal Editors (ICMJE) guidelines without specifying a version or set of criteria.
- Other administrative corrections were made throughout the protocol.

Amendment 3

Title: A Phase 2 Open Label Extension Study of Conatumumab and AMG 479

Amgen Protocol Number (Conatumumab and AMG 479) 20101116

Amendment Date: 20 December 2012

Rationale:

The protocol was amended to incorporate the following changes:

- Update the sponsor contact information.
- Revise the eligibility criteria, patient population, and treatment procedures to allow 2 ongoing subjects on the AMG 479 20050118 study to rollover into 20101116 study in order to continue to receive AMG 479 at the same dose and schedule they were receiving at the conclusion of the 20050118 Study.
- SAE Reporting Procedures:
    - Change the SAE reporting timelines from 1 working day to 24 hours of discovery to comply with the EU Clinical Trial Guidance on the collection of adverse event/reaction arising from clinical trials.
    - Remove the language that requires the investigator to report SAEs related to investigational products that occurs outside the protocol-specified reporting period since the investigators may use their discretion to report any SAE to Amgen after the safety follow-up, whether related to investigational product or not.
    - Revise the language related to determination of expectedness for expedited reporting of adverse events in clinical trials to ensure better alignment with ICH E6 and regulatory agency expectations.
- Add lactation reporting procedures and the Lactation Notification Worksheet.

Amendment 2

Protocol Title: A Phase 2 Open Label Extension Study of Conatumumab

Amgen Protocol Number AMG 655 (Conatumumab) 20101116

EudraCT number: 2010-022270-14

Amendment Date: 25 January 2012

Rationale:

The protocol has been amended for the following reasons:

- To update the conatumumab investigational product information due to the transition of the conatumumab clinical supply for this study from material manufactured by Process 1 to material manufactured by Process 2. The change in clinical supply eliminates the risk caused by the potential for the Process 1 material to form flake-like glass particles when stored at -70°C. Process 2 material is stored and shipped at refrigerated conditions, and therefore does not form flake-like glass particles, and does not require the use on an in-line filter.
- To remove the requirement for the use of an in-line, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron filter when administering conatumumab investigational product. Filter use is not required for intravenous infusion of conatumumab Process 2 material.
- To revise the sample size from approximately 50 to 15 subjects because fewer than expected subjects decided to continue treatment on this rollover study.
- To add new section (Section 9.3) to provide instructions for pregnancy reporting.
- To replace Pregnancy Notification Form with current Form.
- To update the sponsor contact information.
- Finally, minor administrative errors in the protocol were corrected.

Amendment 1

Protocol Title: A Phase 2 Open Label Extension Study of Conatumumab

Amgen Protocol Number: AMG 655 (Conatumumab) 20101116

Amendment Date: 25 May 2011

Rationale:

The protocol has been amended for the following reasons:

- The purpose of this protocol amendment is to add a requirement for the use of an in-line, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron filter when administering AMG 655 and AMG 479 investigational product. Notification to investigators of this requirement was provided in the form of a letter dated 27 May 2011. Filter use is being implemented to address a potential risk of formation of particles in vials of AMG 655 and AMG 479 investigational product that has been exposed to temperatures of -30°C or lower.
- Provide minor procedural clarifications
- Updated sponsor contact information

Section: Global

Replace: 07 September 2010

With: **25 May 2011**

Section: Title page

Replace:

[redacted], PT
Clinical Research Study Manager
Amgen Inc.
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

With:

[redacted]
Clinical Research Study Manager
Amgen Inc.
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]