# A Phase II Study of Capecitabine, Carboplatin, and Bevacizumab for Metastatic or Unresectable Gastroesophageal Junction and Gastric Adenocarcinoma

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# PROTOCOL SYNOPSIS

## A Phase II Study of Capecitabine, Carboplatin, and Bevacizumab for Metastatic or Unresectable Gastroesophageal Junction and Gastric Adenocarcinomas

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**Study Center**: Stanford University Medical Center

**Number of subjects planned:** 35

**Planned accrual:**
- 2 patients per month with enrollment complete in 18 months.
- Median time on study estimated at 6 months.
- Median follow-up at time of study completion estimated at 12 months.

**Objectives**

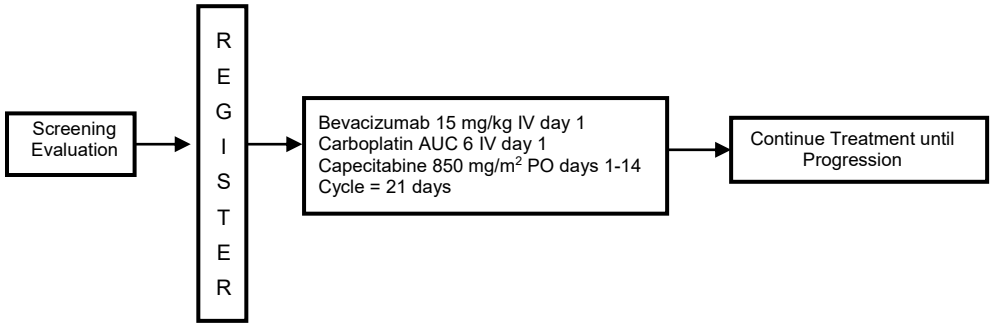
Primary Objectives
- To investigate if the addition of Bevacizumab to standard chemotherapy for metastatic or unresectable GEJ and gastric adenocarcinoma will improve PFS by 90% over historical controls.

Secondary Objectives
- To assess toxicities using CTCAE v3.0
- To evaluate overall survival (OS) using Kaplan-Meier analysis
- To evaluate objective response rate (RR) by RECIST criteria

- To explore biomarkers of tumor response: CEA, CA 19.9, and serum VEGF
- To bank serum and tissue for future correlative studies
- To evaluate CT Perfusion to predict early therapeutic response to combination chemotherapy and anti-angiogenic therapy (OPTIONAL).

**Study Design**

We propose a single-institution, phase II, single-arm, non-randomized study investigating bevacizumab in combination with carboplatin and capecitabine for patients with unresectable or metastatic GEJ or gastric cancers as first-line metastatic therapy. Treatment will be given every 21 days as per the schema outlined below. Patients will receive CT scans at baseline and after every 3 cycles (approximately 9 weeks) and be evaluated by RECIST criteria. We estimate that most patients will complete between 3-6 cycles of treatment. If, after 3 cycles, patients develop significant toxicities attributed to either carboplatin (cytopenias, >2 dose reductions) and/or capecitabine (diarrhea, hand-foot syndrome) patients may discontinue either carboplatin and/or capecitabine and continue receiving . Upon documentation of first disease progression by RECIST criteria, the patient will either restart the original schedule of capecitabine, carboplatin, and or be discontinued from the study, at the investigator's discretion. We will continue treatment indefinitely until one of the following occurs: patient withdraws consent and decides to discontinue study treatment, development of unacceptable toxicities, or evidence for second disease progression (after restarting original schedule as above). The patient may withdraw from the study at any time.




**Target Subject Population:**

Patients with histologically confirmed adenocarcinomas of the gastroesophageal junction (GEJ) or stomach which are deemed unresectable or metastatic will be eligible for enrollment in this study. Patients receiving prior treatment for metastatic disease and/or prior anti-VEGF therapy will be excluded from the study.

**Investigational Products, Dosage and Mode of Administration:**

Capecitabine: 850 mg/m2 PO BID days 1-14 (21-day cycle)
Carboplatin: AUC 6 IV day 1 (21-day cycle)
Bevacizumab: 15 mg/kg IV day 1 (21-day cycle)

**Duration of Treatment:**

Each cycle lasts 21 days. Patients will continue on treatment until one of the following occurs:

- Patient chooses to withdraw from study
- Unacceptable toxicity occurs
- Evidence of progressive disease by RECIST criteria

**Safety:**
Safety assessments will consist of routine and frequent monitoring and recording of all adverse events and serious adverse events, regular monitoring of hematology and serum chemistry, coagulation tests, urinalysis, regular measurement of vital signs, weight, WHO Performance Status and the performance of physical examination. The toxicities experienced by each patient on the study, and the study's overall progress, will be reviewed weekly by the Stanford University Developmental Therapeutics Meeting, chaired by Drs. Branimir Sikic and George Fisher.

**Statistical Methods:**
Data from Kang, et al[1] show that in patients with advanced gastric cancer treated with cisplatin and capecitabine the 6-month progression-free survival (PFS) rate is 50% and the 12-month rate is 24% which we will use as our historical control. We propose a trial of 35 patients with PFS as the primary endpoint and a therapeutic target of increasing the 12-month PFS by 90% to a rate of 46%. If the target is met, there is 80% probability (power) that the 95% lower confidence for PFS at 12-month will lie above the historical rate of 24%.

PFS curves will be generated using Kaplan-Meier method and compared to historical controls using a z-test with Greenwood formula. OS will also be generated using Kaplan-Meier method. RR will be estimated with a binomial confidence interval. CEA will be summarized (mean, standard deviation, median, range) at each time point and then compared with PFS using a log rank test.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADL | Activities of daily living |
| AE | Adverse event |
| ALT/SGPT | Alanine transaminase/Serum glutamate pyruvate transaminase |
| ANC | Absolute neutrophil count |
| AST/SGOT | Aspartate transaminase/Serum glutamic oxaloacetic transaminase |
| BID | Twice daily |
| BSA | Body surface area |
| CBC | Complete Blood Count |
| CI | Confidence interval |
| $C_{max}$ | Maximum concentration of drug |
| CNS | Central Nervous System |
| CRC | Colorectal cancer |
| CRF | Case Report/Record Form |
| CR | Complete response |
| CrCl | Creatinine Clearance |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose Limiting Toxicity |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| EGFR | Epidermal growth factor receptor |
| 5-FU | 5-Fluorouracil |
| G-CSF | Granulocyte colony-stimulating factor (filgrastim) |
| GI | Gastrointestinal |
| Hgb | Hemoglobin |
| HIV | Human Immunodeficiency Virus |
| HPF | High-power field |
| HTN | Hypertension |
| IRB | Institutional Review Board |
| IV | Intravenous(ly) |
| LLN | Lower limit of normal |
| NSCLC | Non-small cell lung cancer |
| OS | Overall survival |
| PLT | Platelet |
| PO | Per os/by mouth/orally |
| PD | Progressive disease |

| | |
|---|---|
| PFS | Progression free survival |
| PR | Partial response |
| PT | Prothrombin time |
| PTT | Partial thromboplastin time |
| QD | Once daily |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RR | Response rate |
| SAE | Serious adverse event |
| SD | Stable disease |
| TTP | Time to progression |
| ULN | Upper Limit of Normal |
| UNK | Unknown |
| VEGF | Vascular Endothelial Growth Factor |
| VEGF-R | Vascular Endothelial Growth Factor Receptor |
| WBC | White Blood Cell |
| WHO | World Health Organization |

# 1.0 BACKGROUND

## 1.1 DISEASE BACKGROUND

Gastroesophageal junction (GEJ) and gastric adenocarcinomas constitute a major health problem worldwide. Gastric cancer is the fourth most prevalent malignancy and the second leading cause of cancer death worldwide[2]. In the United States, an estimated 22,280 cases of gastric cancer were diagnosed and 11,260 patients died from this disease in 2006[3]. Esophageal cancer is overall less common, but the incidence of adenocarcinoma of the esophagus, GEJ and gastric cardia has risen faster than any other malignancy in the last 25 years in the United States and other Western countries[4].

Although treatment for patients with unresectable or metastatic disease remains palliative, chemotherapy improves survival and quality of life when compared to best supportive care[5]. With standard treatment options, the median time to progression for unresectable or metastatic disease is 4 to 6 months and median overall survival is 7 to 10 months.

We propose a single-institution, phase II, single-arm, non-randomized study investigating bevacizumab in combination with carboplatin and capecitabine for patients with unresectable or metastatic GEJ or gastric cancers. We hope that by adding bevacizumab to standard chemotherapy for this patient population we will improve PFS by 90% over historical controls.

## 1.2 BEVACIZUMAB CLINICAL EXPERIENCE

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm (Bevacizumab Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer.

### a. Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF), gastrointestinal perforations, gallbladder perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

**Hypertension**: Hypertension has been commonly seen in bevacizumab clinical trials to date and oral medications have been used to manage the hypertension when indicated. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (Ozcan et al., 2006; Glusker et al., 2006). RPLS may include signs and symptoms of headache, altered mental function, seizures, and visual disturbances / cortical blindness and requires treatment, which should include control of hypertension, management of specific symptoms, and discontinuation of bevacizumab.

**Proteinuria**: Proteinuria has been commonly seen in bevacizumab clinical trials to date. The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1 or 2. In study AVF2107g, none of the 118 patients receiving bolus-IFL plus placebo, three of 158 patients (2%) receiving bolus-IFL plus bevacizumab, and two of 50 (4%) patients receiving 5-FU/LV plus bevacizumab who had a 24-hour collection experienced grade 3 proteinuria (> 3.5 g protein/24 hr). Rare events of nephrotic syndrome have occurred, and bevacizumab should be discontinued in patients with nephrotic syndrome.

**Thromboembolic Events**: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials. In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of **venous TE** events that was not statistically significant in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). There was also a higher rate of **arterial TE** events (3% vs. 1%) such as myocardial infarction, transient ischemia attack, cerebrovascular

accident/stroke and angina/unstable angina**.** A pooled analysis of the rate of arterial TE events from 5 randomized studies (1745 patients) showed that treatment with chemotherapy plus bevacizumab increased the risk of having an arterial TE event compared with chemotherapy alone (3.8% vs. 1.7%, respectively) (Skillings et al., 2005). Furthermore, subjects with certain baseline characteristics (age ≥ 65 years and/or a history of a prior arterial TE event) may be at higher risk of experiencing such an event. . See the bevacizumab Investigator Brochure for additional information on risk factors.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

**Gastrointestinal perforation** Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, and breast) and may be higher in incidence in some tumor types.

**Wound healing complications:** Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone (Scappaticci et al., 2005). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 20 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

**Hemorrhage**: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-associated hemorrhage – was observed in phase I and phase II bevacizumab studies. Six serious events, of which 4 had fatal outcome, were observed in a phase II trial of patients with non-small cell lung cancer receiving bevacizumab. These events occurred suddenly and presented as major or massive hemoptysis in patients with either squamous cell histology and/or tumors located in the center of the chest in close proximity to major blood vessels. In five of these cases, these hemorrhages were preceded by cavitation and/or necrosis of the tumor. Tumor-associated hemorrhage was also seen rarely in other tumor types and locations, including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases and continuous oozing of blood from a thigh sarcoma with necrosis.

Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

**Congestive heart failure**: CHF has been reported in bevacizumab clinical trials and may be increased in incidence in patients with prior exposure to anthracyclines or prior irradiation to the chest wall. In a phase III trial (AVF2119g) of capecitabine with or without bevacizumab for metastatic breast cancer, 7 subjects (3.1%) who received capecitabine plus bevacizumab developed clinically significant CHF compared with 2 subjects (0.9%) treated with capecitabine alone; of note, all subjects in this trial had had prior anthracycline treatment. In addition, 2 subjects had a left ventricular ejection fraction < 50% at baseline and 2 others had prior left chest wall irradiation. A recently published phase II study in subjects with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or decreases to <40% in left ventricular ejection fraction) of 48 subjects treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but one of these subjects had significant prior exposure to anthracyclines as well (Karp et al., 2004). Other studies are ongoing in this patient population. Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA or ECHO with a normal ejection fraction.

**Fistulae**: Patients may be at increased risk for the development of fistulae when treated with bevacizumab. A recent review revealed that most fistulae were involving the GI tract. Among fistulae forms not involving the GI tract, the only fistula event that was not consistent with what would be expected, either by

indication or reporting rate, is tracheoesophageal (TE) fistulae in the small cell lung cancer population. The incidence of GI fistulae and abscess is a bevacizumab ADR of "common" incidence (<2%) in mCRC with the majority of events being of gastrointestinal or genitourinary in nature. It should be noted that most of the patients have significant risk factors that would increase the chance of fistula formation even if they were not receiving bevacizumab. Although fistulae formation is higher with bevacizumab in combination with chemotherapy than with chemotherapy alone, these patients often have multiple risk factors for developing fistulae. Surgery, radiotherapy, and carcinomatosis all predispose both bevacizumab-treated and non–bevacizumab-treated patients to fistula formation. Bevacizumab will be discontinued in patients with TE fistulae or any Grade 4 fistula.

**Ovarian Failure:** The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level≥30 mIU/mL and a negative serum β-HCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n=84 or with bevacizumab (n=95). New cases of ovarian failure were identified in 34% (32/95) of women receiving bevacizumab in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of bevacizumab treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the bevacizumab-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility. Long term effects of the treatment with bevacizumab on fertility are unknown. The risk of ovarian failure will be informed to female with reproductive potential and fertility preservation strategies will be discussed prior to starting treatment with bevacizumab.

**Additional Adverse Events**: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

## 1.3 CAPECITABINE AND CARBOPLATIN CLINICAL EXPERIENCE

There is no formal consensus or evidence-based rationale regarding the best chemotherapy regimen for advanced GEJ and gastric cancer. However, 5-FU has been the backbone of therapy. Parenteral 5-FU has been used since the 1980's to treat advanced GEJ and gastric cancers. In the 1990s, a Phase III trial by Kim, et al[6] demonstrated that 5-FU in combination with cisplatin (FP) had improved response rates when compared with 5-FU monotherapy and combination therapy with 5-FU, doxorubicin and mitomycin (FAM), although overall survival did not differ. Similarly, an EORTC study by Vanhoefer, et al[7] demonstrated a trend towards increased response rates with FP compared with

5-FU, doxorubicin and methotrexate (FAMTX) and etoposide, leucovorin, and bolus 5-FU (ELF).

Capecitabine is an oral fluoropyrimidine that mimics continuous infusion 5-FU and has since replaced it in the treatment of many gastrointestinal malignancies. The conversion to 5-FU is dependent on the enzyme thymidine phosphorylase, which is more highly expressed in tumor tissue than healthy tissue resulting in the preferential generation of 5-FU at the tumor site[8].

Capecitabine is currently approved in the United States for treatment of advanced breast and colorectal cancers and in South Korea for treatment of advanced gastric cancers. Some recent Phase II studies have evaluated the safety and efficacy of capecitabine with cisplatin as first-line treatment of advanced gastric cancer[9-10] and recurrent gastric cancer after fluoropyrimidine-based adjuvant therapy[1]. These studies demonstrated that the combination of capecitabine and cisplatin was well tolerated and active, with TTP and OS equivalent to standard treatments.

Carboplatin is a second generation platinum analogue and has been associated with greater convenience of administration and a more favorable toxicity profile compared to cisplatin. Capecitabine has also been studied in combination with the newer platinum agents, carboplatin[11] and oxaliplatin[12], for the treatment of advanced gastric cancer; these regimen have also demonstrated equivalent safety and efficacy profiles compared to standard treatments.

The combination of carboplatin and capecitabine for metastatic upper GI cancer has been used at our institution and found to have acceptable toxicity and promising anti-tumor activity (retrospective data forthcoming).

## 1.4 STUDY RATIONALE

Bevacizumab in combination therapies is approved for use in the metastatic setting for colorectal[13], breast[14], and lung cancers[15-16]. Bevacizumab in combination with other standard chemotherapies for the treatment of upper gastrointestinal tract adenocarcinomas has shown some early promising data. A Phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or GEJ adenocarcinoma showed improvements in time to progression and overall survival compared to historical controls and was well tolerated[17].

Given the lack of other viable treatment options for metastatic and unresectable GEJ and gastric adenocarcinoma, contrasted with our positive anecdotal experience, we propose a single-institution phase II trial investigating the efficacy of capecitabine, carboplatin and bevacizumab for patients with metastatic GEJ and gastric adenocarcinoma.

## 1.5 CORRELATIVE STUDIES BACKGROUND

- Blood-based assays of angiogenic response.
- CT Perfusion:
  Perfusion computed tomography (CT) imaging has been established for many years in stroke imaging. With the introduction of multi-detector row CT technology increasing substantially the spatial and temporal resolution as well as offering new detector array configurations, CT perfusion imaging has become feasible for assessment of tumor perfusion in applications outside the brain, including the abdomen. Recent studies indicate that perfusion CT can be performed successfully in patients with gastric cancer.[18-19] Different parameters of tumor perfusion have been assessed in patients with gastric cancer and compared to normal gastric tissue including blood flow (BF), blood volume (BV), mean transit time (MTT), time to peak (TTP), permeability surface, and volume transfer constant ($K^{trans}$). The implications of those parameters on grade of tumor vascularization, correlation with ex vivo parameters of angiogenesis including microvessel density (MVD), or expression profiles of molecular markers of tumor angiogenesis such as vascular endothelial growth factor receptor (VEGFR) or integrins in gastric cancer still need to be assessed. However, a recent study in patients with pancreatic endocrine tumors undergoing preoperative perfusion CT has shown high correlation between the tumor BV parameter as assessed by perfusion CT and ex vivo MVD analysis, as well as histoprognostic factors such as proliferation index and WHO classification obtained from tumor samples.[20] Another recent study in patients with locally advanced pancreatic cancer has shown that the parameter $K^{trans}$ may be a valuable quantitative biomarker for predicting favorable treatment response to concurrent chemotherapy and radiotherapy.[21]

  Although the technique of CT perfusion is still evolving and the value of different perfusion parameters in different tumor types still warrants further evaluation, the use of perfusion CT as a non-invasive biomarker to determine treatment response following the application of the vascular disruptive agent ASA404 in gastric cancer patients is intriguing. CT imaging in general is a robust, widely available imaging technology that has been used for cancer imaging for several decades. It is the preferred imaging modality due to its reliability, comparability and robustness. Since the perfusion analysis part of the CT examination can be easily integrated into current CT imaging protocols, there is no need to schedule another exam for a dedicated perfusion exam at the standard baseline and follow-up CT scans in cancer patients.

  In this phase II protocol using capecitabine, carboplatin and bevacizumab for metastatic or unresectable gastroesophageal junction or gastric adenocarcinoma we propose to include CT perfusion imaging as an optional part of the regular CT imaging protocol in patients with gastric cancer. The CT

perfusion part can be included into the standard baseline and 9-week follow-up CT scan. This will not require any additional imaging or radiation exposure.

# 2.0 OBJECTIVES

## 2.1 PRIMARY

- To investigate if the addition of bevacizumab to standard chemotherapy for unresectable and metastatic and GEJ and gastric adenocarcinoma will improve PFS by 90% over historical controls.

## 2.2 SECONDARY

- To assess toxicities using CTCAE v3.0
- To evaluate overall survival (OS) using Kaplan-Meier analysis
- To evaluate objective response rate (RR) by RECIST criteria
- To explore biomarkers of tumor response: CEA, CA 19.9, and serum VEGF
- To bank serum and tissue for future correlative studies
- To evaluate CT Perfusion as a tool to predict early therapeutic response to combination chemotherapy and anti-angiogenic therapy. (participation in this secondary objective is optional)

# 3.0 STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

We propose a single-institution, phase II, single-arm, non-randomized study investigating bevacizumab in combination with carboplatin and capecitabine for patients with unresectable or metastatic GEJ or gastric cancers as first-line metastatic therapy.

All enrolled patients will receive bevacizumab 15 mg/kg intravenously followed by carboplatin AUC 6 intravenously on day 1 of a 21 day cycle. Patients will receive capecitabine 850 mg/m$^2$ twice daily by mouth on days 1-14, followed by a one week break. Patients will be assessed by clinical and laboratory exam at least once per cycle (more frequently as needed) and dose reductions will be allowed

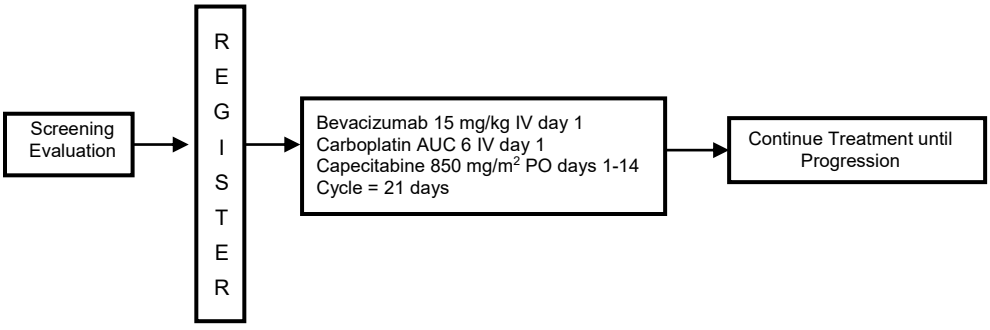
for unacceptable toxicity. Please note that patients may be seen within a 3 day window of the assigned study visit (within 3 days before or 3 days after). Patients will be assessed for response by CT imaging once every 3 cycles (approximately every 9 weeks), or until symptoms suggestive of progressive disease arise.

Standard anti-emetics will be administered to include a 5HT3 antagonist with each dose of chemotherapy. In the event of an infusion reaction with bevacizumab, subsequent doses may be premedicated with diphenhydramine and/or steroid medications.

We estimate that most patients will complete between 3-6 cycles of treatment. If, after 3 cycles, patients develop significant toxicities attributed to either carboplatin (cytopenias, >2 dose reductions) and/or capecitabine (diarrhea, hand-foot syndrome) patients may discontinue either carboplatin and/or capecitabine and continue receiving bevacizumab. Upon documentation of first disease progression by RECIST criteria, the patient will either restart the original schedule of capecitabine, carboplatin, and bevacizumab or be discontinued from the study, at the investigator's discretion. We will continue treatment indefinitely until one of the following occurs: patient withdraws consent and decides to discontinue study treatment, development of unacceptable toxicities, or evidence for second disease progression (after restarting original schedule as above). The patient may withdraw from the study at any time.

If patients with unresectable primary disease have an objective response, they will be referred to surgery for possible resection.

The schema is shown below:




With a planned accrual of 2 patients per month we plan to complete enrollment in 18 months. Median time on study will be estimated to be 6 months, and median follow-up at the time of study completion is estimated to be 12 months.

## 3.2 RATIONALE FOR STUDY DESIGN

Our planned doses, Carboplatin AUC 6 given IV every 21 days and Capecitabine 850 mg/m2 PO BID days 1-14 repeated every 21 days, are standard dosing regimen in GI and other malignancies.

The study by Shah, et al[17] in metastatic gastric and gastroesophageal junction adenocarcinoma, and other studies in lung[15-16] and metastatic colorectal[22] have all used a bevacizumab dose of 5 mg/kg/week IV dose. The study in non-small call lung cancer by Johnson, et al did not find a significant difference in toxicity profiles between a 7.5 mg/kg and 15 mg/kg dose and found a trend towards improved time to progression with the higher dose. Overall, across studies, no dose related adverse events have occurred. We will also use the 5 mg/kg/week dose in our protocol with a specific schedule of 15mg/kg every 21 days.

## 3.3 OUTCOME MEASURES

### 3.3.1 Primary Outcome Measures

- PFS

### 3.3.2 Secondary Outcome Measures

- OS
- RR
- Biomarkers (CEA, CA 19.9, VEGF), evaluated as dichotomous variables

### 3.3.3 Safety Outcome Measures

Toxicities will be assessed per CTCAE v3.0. As bevacizumab administration has been associated with hemorrhage (particularly hemoptysis) and thromboembolic events, we will monitor for these events. In addition, patients will be monitored for systemic, renal, gastrointestinal, hematologic, neurological and liver toxicities. Specifically, patients will have laboratory tests (including CBC with differential, basic metabolic panel, calcium, magnesium and liver function tests) performed every 3 weeks. In addition, patients will be seen in the clinic for history and physical and assessed for side effects and toxicities every 3 weeks.

### 3.3.4 Correlative Outcome Measures

- Serum will be banked for future testing of angiogenesis factors (collected at baseline and with each cycle)
- Tissue will be banked for future testing (collected at baseline and at time of progression by endoscopic biopsy if clinically indicated)
- CT Perfusion (OPTIONAL) will be performed to assess tumor blood flow (performed at baseline and after 3 cycles)

# 4.0 SAFETY PLAN

## 4.1 GENERAL PLAN TO MANAGE SAFETY

### 4.1.1 Bevacizumab-Specific

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 5.3) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements (see Section 7.0). Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 7.1.4).

Specific monitoring procedures are as follows:

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- Proteinuria will be monitored by urine protein: creatinine (UPC) ratio or dipstick at least every 6 weeks.
- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk after surgery).

**Other Study Drug(s)-Specific**

Please see Section 6.1 for detailed instructions for the management of study drug–related toxicities.

### 4.1.2 Capecitabine-Specific

Please see Section 6.2 for the management of capecitabine toxicity.

### 4.1.3 Carboplatin-Specific

Please see Section 6.3 for the management of carboplatin toxicity

## 4.2 DEFINITION OF A DOSE LIMITING TOXICITY (DLT)

The definition of DLT will be any adverse event occurring during the first cycle of treatment that can be causally related to the study treatments and that meets the criteria as described below in this section. See Sections 6.1, 6.2, 6.3 for dose modifications when toxicities are encountered. All toxicity in this study will be graded according to the NCI Common Toxicity Criteria Adverse Events (CTCAE) version 3.0.

**Hematologic toxicity**: Hematologic DLT will be defined as CTCAE grade 4 neutropenia (< 500/mm$^3$) lasting > 5 days, CTCAE grade 4 neutropenia of any duration if associated with fever, CTCAE grade 4 anemia (< 6.5 g/dl) of any duration, or CTCAE grade 4 thrombocytopenia (< 25,000/mm$^3$) of any duration.

**Hepatic toxicity**: An elevation to CTCAE ≥ grade 3 toxicity in one or more liver function tests (bilirubin, AST, or ALT) will be considered a DLT. If liver metastases are present, and the enrollment liver function test in question is above the institutional normal, elevations will be considered a DLT as follows:

- For serum bilirubin an elevation of ≥ 3 times the enrollment value will be considered a DLT (note that patients with liver metastases and serum bilirubin ≤ 3x ULN are eligible for the study).
- For AST and ALT an elevation of ≥ 5 times the enrollment value will be considered a DLT (note that patients with liver metastases and serum AST or ALT of ≤ 5x ULN are eligible for the study).
- If the elevation in liver function test is attributed to a cause other than study treatment (e.g. occlusion of biliary stent or reactivation of viral hepatitis), then study treatment may be held while the cause is addressed, but this will not be considered a DLT.

**Electrolytes**: CTCAE ≥ grade 3 toxicity of electrolytes will be considered a DLT with the following notable exceptions:

- If the toxicity is attributed to a cause other than study treatment, then study treatment may be held while the cause is addressed, but this will not be considered a DLT
- CTCAE grade 3 hypokalemia (2.5-3.0 mmol/L) will not be considered a DLT unless it persists for one week despite appropriate medical management. CTCAE grade 4 hypokalemia will be considered a DLT upon first occurrence.
- Asymptomatic CTCAE grade 3 hyponatremia (120-130 mmol/L) will not be considered a DLT. CTCAE grade 4 hyponatremia will be considered a DLT upon first occurrence.

**Nausea, vomiting and diarrhea**: CTCAE grade 3 nausea, vomiting or diarrhea will be considered a DLT only if the adverse event occurs and persists > 24 hours

despite institution of appropriate and adequate supportive measures (e.g. antiemetics and antidiarrheal medications). Any CTCAE grade 4 nausea, vomiting or diarrhea (characterized by life-threatening consequences) will be considered a DLT.

**Hypertension**: Any elevation in blood pressure deemed by the treating physician to require immediate/urgent lowering of blood pressure, and lasting > 24 hours despite optimization of their antihypertensive medication regimen, will be considered a DLT and result in a treatment interruption. Please refer to Section 7.1.3 for bevacizumab dose modifications. Management of hypertension during the interruption period and remainder of the study period will be at the discretion of the treating physician.

**Ataxia/dizziness and other neurologic toxicity:** CTCAE grade 3 ataxia/dizziness or other grade 3 neurologic toxicity will be considered a DLT if persistent > 10 days with continued dosing of study agents. If the toxicity begins during the first cycle of treatment, and the 10 day symptomatic period extends into cycle 2, the toxicity will still be considered a DLT associated with the first cycle of treatment. CTCAE grade 4 ataxia/dizziness or other grade 4 neurologic toxicity will be considered a DLT regardless of duration.

**Gastrointestinal Perforation:** Any gastrointestinal perforation ≥ CTCAE grade 2 will be considered a DLT.

**Fistulae**: Bevacizumab will be discontinued permanently for all grades of tracheoesophageal fistulae or any grade 4 non-TE fistulae.

**All other study treatment related toxicities**: Any other adverse event, excluding fatigue, directly attributed to the study medications that are ≥ CTCAE grade 3 will be considered a DLT. At the investigator's discretion, administration of the study treatment may be delayed for any toxicity encountered (any CTCAE grade) in the best interests of the patient. Any treatment-related toxicity resulting in a treatment delay of > 14 days will be considered a DLT.

# 5.0 STUDY SUBJECTS

## 5.1 SUBJECT SELECTION

Patients with histologically confirmed adenocarcinoma of the GEJ or stomach which are deemed unresectable or metastatic will be eligible for enrollment in this study. This study is open to both men and women and to all racial/ethnic groups. According to most recent studies on gastrointestinal cancer, there is no evidence for outcome to be affected by either race or gender. Thus, this study will not have separate accrual targets for these different subgroups.

## 5.2 INCLUSION CRITERIA

1. Patients with histologically or cytologically confirmed adenocarcinoma of the GEJ or stomach.
2. Patients must be deemed unresectable due to involvement of critical vasculature or adjacent organ invasion. If unresectable, patients must show evidence of disease progression prior to enrollment.
3. Patients with prior surgical resection who develop radiological or clinical evidence of metastatic cancer do not require separate histological or cytological confirmation of metastatic disease unless an interval of > 5 years has elapsed between the primary surgery and the development of metastatic disease. Clinicians should consider biopsy of lesions to establish diagnosis of metastatic disease if there is substantial clinical ambiguity regarding the nature or source of apparent metastases.
4. Prior carboplatin as neoadjuvant or adjuvant therapy will be allowed if ≥ 6 months from the time of study entry.
5. If patients use aspirin (>325mg/day) or NSAIDS at the time of enrollment, they must have a 10 day washout period prior to beginning protocol treatment.
6. Low molecular weight heparin (or its equivalent, excluding warfarin) will be allowed for treatment of venous thromboembolic events if patients have no evidence of bleeding on full-dose anticoagulation.
7. Patients must have a primary or metastatic lesion measurable in at least one dimension by Modified RECIST criteria (see Section 11.2.3) within 4 weeks prior to entry of study
8. Patients must have ECOG performance status of 0-1
9. Patients must be ≥ 18 years of age
10. Laboratory values ≤ 2 weeks prior to randomization:
    - Absolute Neutrophil Count (ANC) ≥ 1.5 x 109/L (≥ 1500/mm3)
    - Platelets (PLT) ≥ 100 x 109/L (≥ 100,000/mm3)
    - Hemoglobin (Hgb) ≥ 9 g/dL
    - Serum creatinine ≤ 1.5 x ULN
    - Serum bilirubin ≤ 1.5 x ULN (≤ 3.0 x ULN if liver metastases present)
    - Aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT) ≤ 3.0 x ULN (≤ 5.0 x ULN if liver metastases present). Note: ERCP or percutaneous stenting may be used to normalize the liver function tests.
11. Life expectancy ≥ 12 weeks
12. Ability to give written informed consent according to local guidelines

## 5.3 EXCLUSION CRITERIA

### a. Disease-Specific Exclusions

1. Prior chemotherapy for metastatic disease
2. Prior full field radiotherapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior to enrollment. Patients must have recovered from all therapy-related toxicities. The site of previous radiotherapy should have evidence of progressive disease if this is the only site of disease.
3. Prior biologic or immunotherapy ≤ 2 weeks prior to registration. Patients must have recovered from all therapy-related toxicities
4. Prior therapy with anti-VEGF agents
5. If history of other primary cancer, subject eligible only if she or he has:
   - Curatively resected non-melanomatous skin cancer
   - Curatively treated cervical carcinoma in situ
   - Other primary solid tumor curatively treated with no known active disease present and no treatment administered for the last 3 years
6. Concurrent use of other investigational agents and patients who have received investigational drugs ≤ 4 weeks prior to enrollment.
7. Hypersensitivity to capecitabine, fluorouracil, or any component of the formulation and or a known deficiency of dihyropyrimidine dehydrogenase.

### b. General Medical Exclusions

1. Subjects known to have chronic or active hepatitis B or C infection
2. History of any medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risks associated with study participation or study drug administration or may interfere with the conduct of the study or interpretation of study results
3. Male subject who is not willing to use adequate contraception upon enrollment into this study and for 6 months following the last dose of second-line treatment
4. Female subject (of childbearing potential, post-menopausal for less than 6 months, not surgically sterilized, or not abstinent) who is not willing to use an oral, patch or implanted contraceptive, double-barrier birth control, or an IUD during the course of the study and for 6 months following the last dose of second-line treatment
5. Female subject who is breast-feeding or who has positive serum pregnancy test 72 hours prior to randomization
6. Pleural effusion or ascites that causes respiratory compromise (≥ CTCAE grade 2 dyspnea)

7. Any of the following concurrent severe and/or uncontrolled medical conditions within 24 weeks of enrollment which could compromise participation in the study:

   - Unstable angina pectoris
   - Symptomatic congestive heart failure
   - Myocardial infarction ≤ 6 months prior to registration and/or randomization
   - Serious uncontrolled cardiac arrhythmia
   - Uncontrolled diabetes
   - Active or uncontrolled infection
   - Interstitial pneumonia or extensive and symptomatic interstitial fibrosis of the lung.
   - Chronic renal disease
   - Acute or chronic liver disease (e.g., hepatitis, cirrhosis)

8. Patients unwilling to or unable to comply with the protocol

9. Current, recent (within 4 weeks of the first infusion of this study), or planned participation in an experimental drug study other than a Genentech-sponsored bevacizumab cancer study

**c. Bevacizumab-Specific Exclusions**

1. Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure > 100 mmHg on antihypertensive medications)
2. Any prior history of hypertensive crisis or hypertensive encephalopathy
3. New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix A)
4. History of myocardial infarction or unstable angina within 6 months prior to study enrollment
5. History of stroke or transient ischemic attack within 6 months prior to study enrollment
6. Known CNS disease, brain metastases.
7. Significant vascular disease (e.g., aortic aneurysm, aortic dissection)
8. Symptomatic peripheral vascular disease
9. Evidence of bleeding diathesis or coagulopathy

10. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study enrollment or anticipation of need for major surgical procedure during the course of the study
11. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to study enrollment
12. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment
13. Serious, non-healing wound, ulcer, or bone fracture
14. Urine protein ≥ 2+ on urinalysis dipstick and ≥ 1.0 gram on 24-hour urine collection
15. Known hypersensitivity to any component of bevacizumab
16. History of GI bleeding (hemoptysis/melena/hematochezia, $\geq$ 1/2 teaspoon of bright red blood per episode) within 3 month prior to Day 1.
17. Current, ongoing treatment with full-dose warfarin.

# 6.0 STUDY MEDICATION

## 6.1 BEVACIZUMAB

### 6.1.1 Bevacizumab Dosage and Formulation

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 5-cc (100-mg) and 20-cc (400-mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only. For further details and molecule characterization, see the bevacizumab Investigator Brochure.

### 6.1.2 Bevacizumab Administration

Bevacizumab will be administered at a dose of 15 mg/kg intravenously on day 1 of a 21-day cycle.

Bevacizumab will be diluted in a total volume of 100mL of 0.9% Sodium Chloride Injection, USP. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration.

The initial dose will be delivered over 90$\pm$15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60$\pm$10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30$\pm$10 minutes.

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be premedicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

### 6.1.3 Bevacizumab Storage

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

### 6.1.4 Bevacizumab Dose Modification and Toxicity Management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Infusion Reaction: Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 3.0 Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 1.

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 2 months.

**Table1: Bevacizumab Dose Management Due to Adverse Events**

| Event | Action to be Taken |
|---|---|
| **Hypertension** | |
| No dose modifications for grade 1/2 events | |
| Grade 3 | If not controlled to 150/100 mmHg with medication, discontinue bevacizumab. |
| Grade 4 (including RPLS (confirmed by MRI) or hypertensive encephalopathy) | Discontinue bevacizumab. |
| **Hemorrhage** | |
| No dose modifications for grade 1/2 nonpulmonary and non-CNS events | |
| Grade ≥ 2 pulmonary or CNS hemorrhage | Discontinue bevacizumab. |
| Grade 3 nonpulmonary and non-CNS hemorrhage | Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab.<br>All other subjects will have study treatment held until all of the following criteria are met:<br>• The bleeding has resolved and hemoglobin is stable.<br>• There is no bleeding diathesis that would increase the risk of therapy.<br>• There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.<br>Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab. |
| Grade 4 | Discontinue bevacizumab. |

**Table 1: Bevacizumab Dose Management due to Adverse Events cont'd**

**Table 1: Bevacizumab Dose Management due to Adverse Events cont'd**

| | |
|---|---|
| **Venous Thrombosis** | |
| No dose modifications for grade 1/2 events | |
| Grade 3/ Asymptomatic Grade 4 | Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, study drug should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, study drug may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:<br>• The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.<br>• The subject must not have had evidence of tumor involving major blood vessels on any prior CT scan.<br>• As per exclusion criteria, warfarin is not allowed |
| Symptomatic Grade 4 | Discontinue bevacizumab. |
| **Arterial Thromboembolic event** | |
| (Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event) | |
| Any grade | Discontinue bevacizumab. |
| **Congestive Heart Failure (Left ventricular systolic dysfunction)** | |
| No dose modifications for grade 1/2 events | |
| Grade 3 | Hold bevacizumab until resolution to Grade ≤ 1. |
| Grade 4 | Discontinue bevacizumab. |
| **Proteinuria** | |
| Grade 1 | No bevacizumab dose modifications |
| Grade 2 | Hold bevacizumab for ≥ 2 grams/24 hours, and resume when proteinuria is < 2 grams/24 hours<br>For 2+ dipstick: May administer bevacizumab; obtain 24 hour urine prior to next bevacizumab dose.<br>For 3+ dipstick: Obtain 24 hour urine prior to bevacizumab administration |
| Grade 3 | Hold bevacizumab. Resume when proteinuria is < 2 grams/24 hours |
| Grade 4 (nephrotic syndrome) | Discontinue bevacizumab |
| **GI Perforation** | Discontinue bevacizumab. |

| Table 1: Bevacizumab Dose Management due to Adverse Events cont'd | |
|---|---|
| **Bowel Obstruction** | |
| Grade 1 | Continue patient on study for partial obstruction NOT requiring medical intervention. |
| Grade 2 | Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution. |
| Grade 3/4 | Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion. |
| **Wound dehiscence** requiring medical or surgical therapy | Discontinue bevacizumab. |
| **Other Unspecified Bevacizumab-Related Adverse Events** | |
| Grade 3 | Hold bevacizumab until recovery to ≤ Grade 1 |
| Grade 4 | Discontinue bevacizumab. |

## 6.2 CAPECITABINE

### 6.2.1 Capecitabine Administration

Capecitabine is a fluoropyrimidine carbamate that is an orally active prodrug of 5-fluorouracil. Normal cells, as well as tumor cells metabolize 5- fluorouracil into 5-fluoro-2'deoxyuridinemonophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). Both are metabolites that cause cell injury by two different mechanisms. FdUMP and the folate factor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to inhibit the formation of thymidylate. This deficiency of thymidylate causes cell cycle division to halt. This is because thymidylate is necessary for thymidine triphosphate production, which is essential for DNA synthesis. FUTP works by incorporating itself into transcription in place of uridine triphosphate therefore interfering with RNA transcription and protein synthesis.

Capecitabine is supplied as biconvex, oblong film-coated tablets, available as 150 mg tablets (light peach) and 500 mg tablets (peach). Capecitabine tablets should be swallowed with water within 30 minutes after a meal. The calculated dose by body surface area (BSA) will be rounded down to allow equivalent morning and evening doses using a combination of 150 mg and 500 mg tablets.

Capecitabine will be administered at an initial dose of 850 mg/m2 by mouth twice daily, on days 1-14 of a 21-day cycle.

### 6.2.2 Capecitabine Storage

Capecitabine is stored at 25 °C, with excursions permitted to 15 to 30 °C.

### 6.2.3 Capecitabine Drug Interactions

Capecitabine $C_{max}$ and AUC have been shown to increase by approximately 20-35% when given concurrently with antacids. Therefore administration of capecitabine should be separated by two hours from any antacids.

Capecitabine increases the serum level of warfarin with concomitant administration. Therefore, a patient who takes both requires more frequent testing of INR and PT so the appropriate dose adjustment can be made.

Capecitabine also increases the serum level of phenytoin. The patient may need more frequent monitoring of phenytoin levels so dosing adjustments can be made appropriately.

Capecitabine has not been shown to interact with CYP450 isoenzymes although extra care should be expressed when administering CYP2C9 substrates.

### 6.2.4 Capecitabine Dose Modification and Toxicity Management

Potential toxicities of capecitabine are as follows:

**Hematologic:** anemia, neutropenia

**Constitutional:** fatigue, pyrexia, edema, pain, chest pain

**Dermatologic:** hand-foot syndrome, dermatitis, skin discoloration, alopecia

**Gastrointestinal:** diarrhea, nausea, vomiting, stomatitis, abdominal pain, gastrointestinal motility disorder, constipation, oral discomfort, upper GI inflammatory disorders, gastrointestinal hemorrhage, ileus

**Hepatic:** hyperbilirubinemia

**Infections:** bacterial or viral

**Metabolic:** appetite decreased, dehydration

**Musculoskeletal:** back pain, arthralgia

**Neurologic:** peripheral sensory neuropathy, headache, dizziness, insomnia, taste disturbance

**Ocular:** eye irritation, vision abnormal

**Psychiatric:** mood alteration, depression

**Pulmonary:** dyspnea, cough, pharyngeal disorder, epistaxis, sore throat

**Vascular:** venous thrombosis

A dose reduction will be instituted upon any grade 3 or 4 toxicity that is attributable to capecitabine. If there is uncertainty as to which agent in the

treatment regimen is responsible for a particular toxicity, then the particular agent reduced will be at the investigator's discretion.

For all grade 3 or 4 toxicities related to capecitabine, the study treatment will be withheld for up to 3 weeks until the toxicity has resolved to CTCAE grade 1 or better, and then treatment may be restarted. Dose reduction/re-challenge for each toxicity criterion will be managed as discussed in the sections that follow. Patients will be withdrawn from the study if toxicity does not resolve to $\leq$ CTCAE grade 1 within 3 weeks.

**Myelosuppression**

On Day 1 of each cycle, if the neutrophil count is < 1500/$mm^3$, or the platelet count is < 100,000/$mm^3$, then treatment with carboplatin, capecitabine, and bevacizumab will be held until the neutrophil count is ≥ 1500/$mm^3$, and platelet count is ≥ 100,000/$mm^3$. If treatment is required to be held for ≥ 3 weeks, then study treatment will be discontinued. Refer to section 6.3.2 for carboplatin dose adjustments to carboplatin for myelosuppression.

The investigator(s) may allow a patient to continue on bevacizumab if initiation of the next carboplatin treatment is delayed due to the presence of myelosuppression.

**GI Toxicity**

Nausea, vomiting, or both may be controlled with antiemetic therapy. Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits. Patients who are clinically unstable because of diarrhea or other intercurrent medical illness must be admitted and evaluated using telemetry, until clinically stable.

Dose modifications for diarrhea will be as follows:

If ≥ grade 3 diarrhea refractory to oral anti-diarrheal medication occurs, all treatment will be held until the toxicity is < grade 2, then the capecitabine dosage will be reduced according to Table 2 shown below:

**Table 2. Capecitabine dose modification**

| Starting Capecitabine Dose | 1st Reduction | Incremental Percent Reduction | 2nd Reduction | Incremental Percent Reduction |
|---|---|---|---|---|
| 1000 mg BID | 1000 mg AM<br>650 mg PM | 18% | 650 mg AM<br>650 mg PM | 21% |
| 1500 mg AM<br>1000 mg PM | 1000 mg BID | 20% | 1000 mg AM<br>650 mg PM | 18% |
| 1500 mg BID | 1500 mg AM<br>1000 mg PM | 17% | 1000 mg BID | 20% |
| 2000 mg AM<br>1500 mg PM | 1500 mg AM<br>1300 mg PM | 20% | 1150 mg AM<br>1150 mg PM | 18% |
| 2000 mg BID | 1650 mg AM<br>1500 mg PM | 21% | 1500 mg AM<br>1000 mg PM | 20% |

If ≥ grade 3 diarrhea occurs after the first capecitabine dose reduction, then treatment will be held until the toxicity is < grade 2 and then a second capecitabine dose reduction according to Table 2 will be instituted. If ≥ grade 3 diarrhea occurs following 2 capecitabine dose reductions, then treatment will again be held until the toxicity is < grade 2, then treatment will resume at the same doses except that the carboplatin dosage will be reduced by 20%. If ≥ grade 3 diarrhea persists, patients will be withdrawn from the study.

If treatment must be withheld for more than 3 weeks for resolution of diarrhea, the patient will not restart treatment with study medication and the patient will be withdrawn from the study.

### Mucositis or Hand/Foot Syndrome (HFS)

If ≥ grade 3 mucositis or HFS occurs, capecitabine will be interrupted for a minimum of 1 week. If the toxicity has not improved to < grade 2, the treatments will be held for up to 2 additional weeks. Once restarted, the dose of capecitabine will be reduced according to Table 2. Beyond two dose reductions, if further toxicity is encountered, the patient will be discontinued from study treatment.

### Other toxicities

If ≥ grade 3 toxicities directly attributable to capecitabine other than those discussed above occur (except fatigue, alopecia, or nausea/emesis in the absence of anti-emetics), therapy will be discontinued until the toxicity is < grade 2. If there is no evidence of tumor progression, therapy may resume with a dose reduction according to Table 2.

## 6.3 CARBOPLATIN

Carboplatin is a second generation platinum analogue and has been associated with greater convenience of administration and a more favorable toxicity profile compared to cisplatin. Carboplatin is commercially available agents and further details regarding storage, administration, dose modification and toxicity management can be obtained in the package inserts.

### 6.3.1 Carboplatin Administration

The carboplatin dose will be based on the Calvert formula (Appendix E) and given at a target area under the curve (AUC) of 6 mg/mL x min and glomerular filtration rate (GFR) estimated for males as GFR = (140-age) x weight/72 x (serum creatinine). For females, a correction factor of 0.85 will be used (Appendix E). The initial dose weight will be used. Carboplatin will be administered over 30-60 minutes on day 1 every 21 days.

### 6.3.2 Carboplatin Dose Modification and Toxicity Management

**Table 3: Carboplatin dose modifications**

| **Toxicity** | **Carboplatin** |
|---|---|
| ANC≥1500<br>Platelets≥100,000 | Full dose |
| ANC≥1000 but <1500<br>Platelets≥10,000 but <100,000 | Delay chemotherapy by one week and reduce subsequent dose by 20%*† |
| ANC<1000<br>Platelets<10,000 | Delay chemotherapy by one or more weeks and reduce subsequent dose by 20%*†, growth factors may be given as clinically indicated. |
| *If patient requires >2 reductions for neutropenia and thrombocytopenia within first 3 cycles, the patient will be taken off study. If this occurs after 3 cycles patients may discontinue carboplatin and continue receiving bevacizumab with or without capecitabine (as per study design). Upon documentation of first disease progression by RECIST criteria, the patient will either restart the original schedule of capecitabine, carboplatin, and bevacizumab or be discontinued from the study, at the investigator's discretion. If the patient has persistent neutropenia and/or thrombocytopenia for more than 3 weeks he/she will be taken off study.<br>†Carboplatin dose reductions will be a percentage reduction of prior AUC (ie. If patient started at AUC 6, a 20% dose reduction would be an AUC of 4.8) or prior total dose in milligrams whichever is lower.<br>Note: growth factors may be used at investigator's discretion. | |

## 6.4 GENERAL DOSE MODIFICATIONS

Dose will be modified for all three drugs if there is 10% change in patient's weight while on study.

Any of the three drugs can be discontinued at the investigator's discretion for any adverse event with severity of grade 3 or more

If patient is in confirmed Complete Remission (CR) for a period of 18 weeks or more, investigator may give chemotherapy break; surveillance CT scan every 9 weeks will be continued. Upon documentation of first disease progression by RECIST criteria, the patient will restart chemotherapy, at the investigator's discretion.

If patient is on maintenance Bevacizumab, upon documentation of first disease progression by RECIST criteria, the patient will restart the original schedule of Capecitabine, Carboplatin, and Bevacizumab, at the investigator's discretion.

## 6.5 CONCOMITANT MEDICATIONS

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form. All supportive care measures consistent with optimal patient care will be given throughout the study. Patients should be maintained on the same medications throughout the study period, if medically appropriate. All medications taken within 30 days of the screening visit should be recorded on the data collection forms. All cancer medications/therapies given to the patient within 28 days after the last dose of study drug must also be recorded on the data collection forms.

- Other chemotherapy, investigational agents, radiation or biologic therapy may not be used while the patient is in this study.
- Hematologic growth factors are not part of this study. However, growth factor support for anemia and/or neutropenia will be at the discretion of the treating physician and should be documented.
- Megace can be used for appetite support and needs to be reported on the case report forms.
- No data exists regarding the interaction of the study medications with commonly used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving study treatment.

- Low-dose aspirin (≤ 325 mg/d) may be continued in subjects at higher risk for arterial thromboembolic disease. Subjects developing signs of arterial ischemia or bleeding on study should be evaluated for possible bevacizumab discontinuation per Table 1, Bevacizumab Dose Management Due To Adverse Events.

# 7.0 CLINICAL AND LABORATORY EVALUATIONS

## 7.1 STUDY SCHEDULE

| **Cycle** | **Screen** | **1** | **2** | **3** | **Withdrawal of Study treatment** |
|---|---|---|---|---|---|
| **Week** | **0** | **1** | **4** | **7** | |
| **Day[d]** | **0** | **1** | **1** | **1** | |
| Informed consent | X | | | | |
| Medical history | X | X | X | X | X |
| Inclusion/exclusion criteria | X | | | | |
| Physical examination | X | X | X | X | X |
| Vital signs | X | X | X | X | X |
| Hematology/chemistry | X | X | X | X | X |
| Biomarkers[c] | X | X | X | X | X |
| Urinalysis[b] | X | X | | X | X |
| Pregnancy test | X | | | | |
| Performance Status | X | X | X | X | X |
| RECIST | X[a] | | | X[a] | X[a] |
| Tolerability/AE reporting | | X | X | X | X |
| Concurrent medication | X | X | X | X | X |

a- Measurement of tumor will be done at baseline, every 3 cycles (end of cycle 3, 6, 9, etc.) and at withdrawal of study treatment
b- Urinalysis obtained at screening and every other cycle thereafter (cycles 3, 5, 7 etc). If urine dipstick reveals protein ≥ 2+, then 24-hour urine collection will be obtained to quantify proteinuria.
c- Sampling of serum for CEA, CA 19.9, and circulating VEGF levels will be done on the first day of each cycle
d- Patients may be seen within a 3 day window of the assigned study visit.

## 7.2 PRE-TREATMENT EVALUATIONS

- Medical history, physical exam, and assessment of performance status
- Vital signs, including blood pressure
- Blood: Complete blood count with differential, comprehensive metabolic panel, CEA, CA 19.9, VEGF level, and serum banked for future studies.
- Urine: Urinalysis, Pregnancy test if female
- Tissue: Banked for future studies, HER2 status will be also evaluated

- Imaging:
  - Radiographic imaging, CT or MRI preferred, of measurable disease for assessment by RECIST criteria (standard clinical care)
  - CT Perfusion as a correlative study (Optional)

## 7.3 EVALUATIONS DURING TREATMENT

On the first day of each cycle (concurrent with each bevacizumab treatment):

- Medical history and physical exam
- Vital signs, including blood pressure
- Blood: Complete blood count with differential, comprehensive metabolic panel, CEA, CA 19.9, VEGF level, and serum banked for future studies.
- CEA, CA 19.9, VEGF level and serum banking need not be repeated if it is done within last 3 weeks in case of delayed cycle or chemotherapy break.
- Urine for urineanalysis: If dipstick reveals protein ≥ 2+, then 24-hour urine will be obtained to quantify proteinuria. Patient may continue on study if there is < 1.0 gram protein in a 24-hour collection of urine.
- Imaging:
  - CT or MRI scans with measurement of target lesions by RECIST criteria will be done at the conclusion of every 3 cycles (approximately every 9 weeks).
  - CT Perfusion will be performed after 3 cycles as a correlative study. (Optional)

## 7.4 POST-TREATMENT EVALUATIONS

Upon patient withdrawal from study, every effort will be undertaken to obtain the following:

- Medical history and physical exam
- Vital signs, including blood pressure
- Blood: Complete blood count with differential, comprehensive metabolic panel, CEA, CA 19.9, VEGF level, and serum banked for future studies.
- Imaging:
  - CT or MRI scans with measurement of target lesions by RECIST criteria and CT Perfusion (OPTIONAL) as a correlative study will be performed *if not done within 4 weeks prior to withdrawal from study*.

# 8.0 CORRELATIVE/SPECIAL STUDIES

## 8.1 SERUM VEGF

- Collection of Specimen:
  - Plasma (NO HEPARIN)
  - 5 aliquots of 50 microliters each
- Handling of Specimen[23]
- Site Performing Correlative Study:
  - Hanlee Ji, MD PhD
    Assistant Professor of Medicine (Oncology)
    Stanford University Medical School
    [redacted]
    269 Campus Drive
    Stanford, California 94305
    [redacted]
    genomics_ji@stanford.edu

## 8.2 CT PERFUSION (OPTIONAL)

Routine screening procedures for contrast-enhanced CT at all Stanford imaging centers will be followed, with no additional laboratory values obtained for the purposes of this study. Screening for patients undergoing contrast-enhanced CT at Stanford includes but is not limited to questions about prior reactions to intravenous iodinated contrast, possibility of pregnancy, history of diabetes or renal disease, and if greater than 70 years of age, a recent serum creatinine. If any absolute contraindications to contrast-enhanced CT are detected during screening, the patient will be excluded from the study. If needed, the referring clinician will then be contacted.

The duration of each CT scan is approximately 30 minutes. Analysis of each scan for a given participant is estimated to take 30-60 minutes. The participants will also be followed per clinical routine with periodic CT scans until disease progression is detected, which may occur greater than one year following treatment. Thus, while this study is based on data obtained from the first year following treatment, we will also be looking at data from the participant's subsequent CT scans in an exploratory longitudinal study to detect possible relationships between disease progression and changing perfusion characteristics.

On a technical note, previous studies of perfusion CT have been limited by the relatively short scan ranges permitted by available CT scanner models. A new dual-source CT scanner was installed at Stanford in July 2009 that is capable of performing perfusion imaging. Two new dual-source scanners will be installed at Stanford in the Spring 2010 with unprecedented scanning speed and temporal resolution. This speed will allow for perfusion imaging over larger scan ranges, thus making CT perfusion of whole pancreatic tumors possible.

# 9.0 STUDY TREATMENT DISCONTINUATION

Subjects who meet the following criteria should be discontinued from study treatment:

- Disease progression by clinical presentation or by RECIST criteria while on study treatment, at the investigator's discretion.
- Grade 4 hypertension or reversible posterior leukoencephalopathy syndrome (RPLS)
- Nephrotic syndrome
- Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage
- Symptomatic Grade 4 venous thromboembolic event (for lung protocols: any venous thromboembolic event requiring full dose warfarin or equivalent (i.e., unfractionated or low molecular weight heparin)
- Any grade arterial thromboembolic event
- Grade 4 congestive heart failure
- Gastrointestinal perforation
- Wound dehiscence requiring medical or surgical intervention
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- All Grade 4 events thought to be related to bevacizumab by the investigator

Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible (see Section 6.1.3).

# 10.0 STUDY FOLLOW UP

After study treatment discontinued patients will be followed every 6 months till death for disease progression and survival. Discontinuation of the study will be considered after review of the data by the DSMB for any of the following events:

- Major toxicity (i.e. life-threatening hemorrhage) attributable to study treatment.
- Determination by the DSMB that excessive toxicity attributed to the regimen has been identified that does not meet the safety reason 1 above.

# 11.0 STATISTICAL METHODS

## 11.1 DETERMINATION OF SAMPLE SIZE

Data from Kang, et al[1] show that in patients with advanced gastric cancer treated with cisplatin and capecitabine the 6-month progression-free survival (PFS) rate is 50% and the 12-month rate is 24% which we will use as our historical control. We propose a trial of 35 patients with PFS as the primary endpoint and a therapeutic target of increasing the 12-month PFS by 90% to a rate of 46%. If the target is met, there is 80% probability that the 95% lower confidence for PFS at 12-month will lie above the historical rate of 24%. The 95% confidence margin of error for proportions based on 35 patients is at most 18 percentage points.

PFS curves will be generated using Kaplan-Meier method and compared to historical controls using a z-test with Greenwood formula. OS will also be generated using Kaplan-Meier method. RR will be estimated with a binomial confidence interval. CEA will be summarized (mean, standard deviation, median, range) at each time point and then compared with PFS using a log rank test. The correlation of CT Perfusion parameters with PFS will be assessed using the Cox proportional hazards model.

## 11.2 PLANNED EFFICACY EVALUATIONS

### 11.2.1 Primary Efficacy Variables

- PFS

### 11.2.2 Secondary Efficacy Variables

- OS
- RR
- Biomarkers (CEA, CA 19.9, VEGF)

### 11.2.3 Methods of Analysis

**Efficacy Assessment using Response Evaluation Criteria in Solid Tumors Guideline (RECIST v 1.1)[24]**

**Definitions**: At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable:

- Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
    - 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
    - 20mm by chest X-ray.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with P10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging

**Specifications by methods of measurements**

Measurement of lesions:

- All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less.

- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol.

**Tumor response evaluation**

Baseline documentation of 'target' and 'non-target' lesions

- When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

**Response criteria**

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sumdiameters while on study.

For other details and special circumstances of the RECIST guidelines refer directly to reference.

**Table 1 – Time point response: patients with target (+/– non-target) disease.**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

**Definitions of Other Efficacy Markers**

Overall Survival (OS): Time from the date of enrollment to the date of death due to any cause or the last date the patient was known to be alive (censored observation) at the date of data cutoff for the final analysis

Time to Progression (TTP): Time from the date of enrollment to the date of the first observation of documented disease progression or death to due cancer

Progression-Free Survival (PFS): Duration of time from start of treatment to time of documented progression or death.

# 12.0 SAFETY REPORTING OF ADVERSE EVENTS

## 12.1 GENERAL

- **Data and Safety Monitoring Board**
  The status of each patient on the study, and the study's overall progress, will be reviewed regularly. This review will take place at the Stanford University Cancer Center Gastrointestinal Team Meetings, chaired by Dr. George Fisher. In addition, the study will be monitored semi-annually by the Stanford University Data Safety Monitoring Committee.

- **Confidentiality**
  The protection of the patient's identity will be ensured. Patients will be identified by code number and initials only in any publication of data requiring specific patients results. As required by federal law, patient records may be made available to the Food and Drug Administration.

## 12.2 BEVACIZUMAB-SPECIFIC

### 12.2.1 Adverse Event Reporting and Definitions

In the event of an adverse event the first concern will be for the safety of the subject. Investigators are required to report to Genentech Drug Safety ANY serious treatment emergent adverse event (STEAE) as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during Bevacizumab treatment or during a post-treatment follow-up period that (1) was not present at the start of Bevacizumab treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of Bevacizumab treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

### 12.2.2 Reporting of Serious Treatment Emergent Adverse Events

**All STEAEs should be recorded on a MedWatch 3500a Form and faxed to**:

Genentech Drug Safety
[redacted]
(Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

AND:

Study Coordination Center/Principal Investigator
Pamela L. Kunz, MD
Stanford Cancer Center
875 Blake Wilbur Drive
Stanford, CA 94305
[redacted]

AND:

Stanford University IRB

**MedWatch 3500a Reporting Guidelines:**
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500a form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information: Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500a report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500a form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The

subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported.

**Assessing Causality:**

Investigators are required to assess whether there is a reasonable possibility that bevacizumab caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

# 13.0 RETENTION OF RECORDS

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 3 years after the investigation is completed.

# 14.0 REFERENCES/BIBLIOGRAPHY

[Bevacizumab specific references provided as separate document on Bevacizumab diskette]

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# 15.0 APPENDICES

## APPENDIX A: STUDY FLOW CHART/SCHEMA

*[protocol specific ]*

## APPENDIX B: INFORMED CONSENT

*(Provided as separate document on Bevacizumab diskette- do not forward to Genentech for review)*

## APPENDIX C: CURRENT NCI COMMON TOXICITY CRITERIA Version 3.0

*[Provided as separate document on Bevacizumab diskette]*

## APPENDIX D: FDA MEDWATCH 3500a FORM

*[Provided as separate document. on Bevacizumab diskette]*

## APPENDIX E: NEW YORK HEART ASSOCIATION (NYHA) GUIDELINES

*[Provided as separate document on BevacizumabAvastin diskette]*

## APPENDIX F Procedure for obtaining a urine protein : creatinine ratio

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
2) Determine protein concentration (mg/dL)
3) Determine creatinine concentration (mg/dL)
4) Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

## APPENDIX G Formulas for Carboplatin dose calculation

### Cockcroft-Gault Formula for Calculation of Creatinine Clearance

Males: $\frac{(140 - \text{age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ = mL/min

Females: Estimated creatinine clearance for males x 0.85 = mL/min

### Calvert's Formula for the calculation of Carboplatin dose

Carboplatin Dose = (Target AUC) x (GFR + 25)