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The University of Texas M. D. Anderson Cancer Center
Division of Cancer Medicine

Title: **Phase II Study of Bevacizumab Combined with Capecitabine and Oxaliplatin (CAPOX) in Patients with Advanced Adenocarcinoma of the Small Bowel or Ampulla of Vater**

Study Drugs
Bevacizumab (Avastin®)
Capecitabine
Oxaliplatin

Support Provided By
Genentech, Inc.

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1. BACKGROUND

1.1. ADENOCARCINOMA OF THE SMALL BOWEL AND AMPULLA OF VATER

Small bowel adenocarcinoma (SBA) and ampullary adenocarcinoma (AAC) are rare tumors that commonly present with late stage disease and have an overall poor outcome. The estimated incidence of small bowel cancer for 2007 is 5,640 patients with the vast majority presenting with late stage disease.[1] Because of its infrequency, knowledge of its clinical and pathological characteristics is limited. However, considering that the small bowel constitutes 75% of the length and over 90% of the mucosal surface area of the gastrointestinal tract, it is interesting that only 1% to 2% of gastrointestinal malignancies occur in this segment. [2] Unfortunately, most of these tumors produce nonspecific signs and symptoms, making them difficult to diagnose. Indeed, the lethality of small bowel tumors appears to be related in large part to the delay in diagnosis and treatment.

Risk factors for small bowel malignancy include Crohn's disease, familial adenomatous polyposis, celiac disease, cigarette smoking, alcohol consumption, prior peptic ulcer disease, prior colon cancer, and cystic fibrosis. It also appears to be associated with cholecystectomy, immunosuppressive states, ileostomy, duplications of the small bowel, and high fat and protein intake.

The prognosis of patients with SBA is grim. The overall 5 year survival rates range from 5% to 32%.[3-5] Even in the series of Ouriel and Adams, who reported some of the best results, 70% of those with node-negative disease were alive at 5 years, whereas only 13% with node-positive disease were alive at 5 years.[5]

When analyzed stage for stage, survival of patients with SBA is remarkably similar to that of patients with colonic carcinoma.[6] There are other striking similarities between adenocarcinomas of the small and large bowel as well. For example, the incidence of the two diseases is similar from country to country.[7] There are multiple genetic disorders that lead to varying degrees of increased likelihood of developing adenocarcinoma not only in the small bowel and ampulla of Vater, but also in the colon, stomach, and esophagus (i.e., Peutz-Jeghers

Syndrome, familial adenomatous polyposis, attenuated familial adenomatous polyposis, hereditary non-polyposis colorectal cancer). In addition, adenomatous polyps appear to be precursor lesions for adenocarcinomas in both regions of the gastrointestinal tract.[8] Furthermore, patients with SBA are at greater risk of large bowel adenocarcinoma, and vice versa. Moreover, researchers who have identified many of the molecular and genetic changes that occur at various stages in the development and progression of adenoma-carcinoma sequence have noted that the molecular genetic changes, frequencies, and order of appearances of several important oncogenes that occur in colorectal cancer are also seen in small bowel carcinoma.[9, 10] In particular, abnormalities in cyclin D1, p53, MLH-1, MSH-2, APC, CTNNB1 and KRAS are present in both cancers.[11] More specifically, the activating mutations in the KRAS oncogene occur in about 40% of both small bowel and large bowel adenocarcinoma.[12, 13] The level of the p53 protein is also increased in up to 70% of tumors at both sites, with higher levels in adenocarcinomas than adenomatous polyps. The level of the p53 protein is also increased during adenoma-to-carcinoma transition in both large bowel and small bowel adenocarcinoma.

In support of the similarities between small bowel and large bowel adenocarcinoma we have recently demonstrated similar outcomes with the use of capecitabine plus oxaliplatin (CAPOX) chemotherapy. Our response rate of 52% is nearly identical to the expected response rate seen with CAPOX in the treatment of colorectal adenocarcinoma.

1.2 TREATMENT FOR ADENOCARCINOMA OF THE SMALL BOWEL AND AMPULA OF VATER

Systemic chemotherapy has been known to be active in SBA for a number of years. However because of the low incidence of small bowel adenocarcinoma, the literature on the use of chemotherapy in this cancer is sparse. A review of the literature regarding the use of chemotherapy in adenocarcinoma of the small bowel is presented in table 1. The benefit of chemotherapy in advanced small bowel adenocarcinoma has recently been demonstrated. A statistical overall survival benefit with chemotherapy versus no chemotherapy was shown in the MD Anderson Cancer Center retrospective review by Dabaja et. al.[4] Both retrospective studies by Czykowski et. al. and Oriel et. al. demonstrated a trend

to benefit with 5-fluorouracil (5-FU) based chemotherapy but given the small numbers no statistical significance was obtained.[5, 14]

Table 1: Prior studies of Chemotherapy treatment for small bowel adenocarcinoma

Author	Year	study	No. of patients	Chemotherapy	RR	OS (m)
Overman et al.[15]	2009	phase II	30	CAPOX	52%	20.4
Fishman et al.[16]	2006	Retrospective	44	Various agents	29%	18.6
Locher et al.[17]	2005	Retrospective	20	5-FU and platinum	21%	14
Gibson et al.[18]	2005	phase II	38	FAM	18%	8
Czaykowski et al.[14]	2004	retrospective	37	5-FU based	5%	16
Crawley et al.[19]	1998	retrospective	8	ECF/5-FU	37%	13
Jigyasu et al.[20]	1984	retrospective	14	5-FU based	7%	9
Rochlin et al.[21]	1965	retrospective	11	5-FU	36%	NR
Abbreviations: No. (number); 5-FU (5-fluorouracil); RR (response rate); OS (overall survival in months); NR (not reported)						

5-FU, as in colorectal cancer, has remained the backbone chemotherapy agent studied in adenocarcinoma of the small bowel. Response rates observed with primarily single agent 5-FU have varied from 0% to 36%.

Two prospective phase II studies have been conducted in SBA. The first study, conducted by the Eastern Cooperative Oncology Group (ECOG) was reported in 2005. This study defined SBA as adenocarcinoma of duodenum, jejunum, ileum, and ampulla of Vater. The combination of 5-FU, doxorubicin, and mitomycin C (FAM) resulted in an overall response rate of 18.4% and complete response rate of 5%.[18] We have recently completed a phase II study of capecitabine combined with oxaliplatin (CAPOX) in the treatment of SBA and AAC.[15] CAPOX was administered as a 21 day cycle with oxaliplatin 130 mg/m^2 IV administered on day 1 and capecitabine 750 mg/m^2 PO BID administered on days 1-14. This single institution study conducted at M.D. Anderson Cancer

Center enrolled 30 patients with metastatic or unresectable disease over a 31 month time period (11/04 to 7/07). For the 25 patients with metastatic disease the overall response rate was 52%, median progression-free survival (PFS) was 6.6 months and median overall survival was 15.5 months. The six month PFS was 52% (figure 1). Treatment was well tolerated with the most common adverse events being nausea/vomiting, fatigue, and peripheral neuropathy. The most common grade 3/4 toxicities included fatigue in 7 patients (23%), neuropathy in 2 patients (7%), granulocytopenia in 3 patients (10%), vomiting in 3 patients (10%), diarrhea in 3 patients (10%), thrombocytopenia in 2 patients (7%), and hypokalemia in 2 patients (7%). The results of this study have made CAPOX chemotherapy the new standard first-line chemotherapy combination for advanced SBA and AAC.

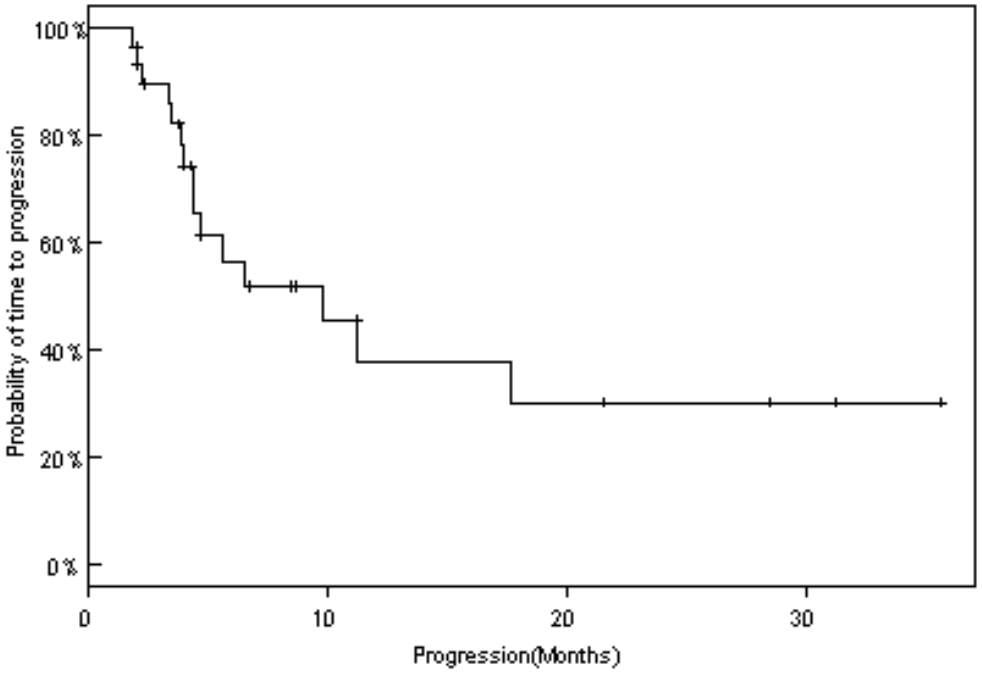


Figure 1. PFS for CAPOX in adenocarcinoma of the small bowel and ampulla of Vater

1.3 VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular endothelial growth factor (VEGF) plays a key role in tumor-associated neo-angiogenesis, which contributes to providing a tumor with oxygen, nutrition, and supports the development of metastases. Binding of VEGF-A to the VEGF receptor (VEGFR) leads to survival, proliferation, and migration of endothelial cells. [22] In addition recent studies have demonstrated the presence of VEGFRs on multiple tumor cells. [23] Increased expression of VEGF has been seen in most human tumors, such as lung, breast, thyroid, colon, and kidney. [24] In xenograft models the inhibition of VEGF signaling results in tumor shrinkage in a wide variety of human cancer cell lines. When inhibition of VEGF signaling is combined with chemotherapy, increased antitumor effects are seen in xenograft models when compared to chemotherapy alone. [25]

1.3.1 VEGF In small bowel adenocarcinoma

No published data exists on the expression of VEGF in small bowel adenocarcinoma. At MD Anderson we have conducted immunohistochemical staining for VEGF-A on 54 SBA tumor samples (unpublished data). In these 54 samples we found VEGF-A to be expressed in 91% of patients. An additional study has also noted universal expression of VEGF-A RNA in a small group of SBA samples.[26] No clinical study has investigated the role of VEGF signaling inhibition in SBA or AAC.

1.4 BEVACIZUMAB

Bevacizumab is an FDA approved recombinant humanized monoclonal IgGF1 antibody that binds to VEGF and prevents the interaction of VEGF to its receptors on endothelial and tumor cells.

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. In addition, data are available from 3,863 patients enrolled in two postmarketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials.

1.5 CAPOX COMBINED WITH BEVACIZUMAB

The combination of CAPOX and bevacizumab has been extensively studied in CRC and has a well defined side effect profile. The randomized phase II TREE

study compared two successive cohorts of patients. In TREE-1 (n=150) patients were treated with either FOLFOX or bolus 5-FU or CAPOX and in TREE-2 (n=223) patients were treated with the same regiments but also received bevacizumab.[27] Capecitabine dosing in TREE-2 was lower than in TREE-1 with capecitabine reduced from 2000mg/m^2/day to 1700mg/m^2/day. The addition of bevacizumab to CAPOX improved outcomes with RR of 46% vs. 27%, median TTP of 10.3 months vs. 5.9 months, and median OS of 24.6 months vs. 17.2 months.

The phase III XELOX-1/NO16966 study, which compared CAPOX to FOLFOX in untreated metastatic colorectal cancer patients, has recently been reported.[28] This was a 1401 patient study in which 654 of the patients also received the addition of bevacizumab to either CAPOX or FOLFOX. The study demonstrated equivalency for these two combinations of fluorinated pyrimidines and oxaliplatin. The primary endpoint was reached with CAPOX demonstrating non-inferiority to FOLFOX for PFS. Both regiments demonstrated good tolerance. Grade 4 toxicities occurred in 12% of the CAPOX arm and 25% of the FOLFOX arm. This difference primarily reflected a difference relating to increased grade 4 neutropenia with FOLFOX. For the FOLFOX arm the most common grade 3-4 toxicities were neutropenia in 43%, diarrhea in 12%, fatigue in 9%, nausea in 5%, and abdominal pain in 5%. The most common grade 3-4 toxicities for the CAPOX arm were diarrhea in 20%, thrombocytopenia in 7%, neutropenia in 7%, hand-foot syndrome in 6%, and fatigue in 6%, and nausea in 5%. The comparison between bevacizumab plus FOLFOX/CAPOX and placebo plus FOLFOX/CAPOX demonstrated similar rates of grade 3-4 toxicity with 21% and 15%, respectively. Grade 3-4 adverse events that were higher with bevacizumab were venous thromboembolism (8% vs. 5%), hypertension (4% vs. 1%), bleeding (2% vs. 1%), and arterial thromboembolic events (2% vs. 1%). The addition of bevacizumab improved outcomes with median PFS of 9.4 months with bevacizumab compared to 8 months with placebo.

1.6 BEVACIZUMAB CLINICAL EXPERIENCE

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.

Additional data from Phase III trials in metastatic CRC (E3200), non–small cell lung cancer (NSCLC; E4599), and metastatic breast cancer (E2100) have also demonstrated clinical benefit from bevacizumab when added to chemotherapy. In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, $HR = 0.75$; $p < 0.01$) in a population of previously treated CRC patients.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; $HR = 0.80$; $p = 0.003$). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006. Finally, patients with untreated metastatic breast cancer (E2100) who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively; $HR = 0.48$; $p < 0.0001$) (see the Bevacizumab Investigator Brochure for additional details).

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) primarily in metastatic breast cancer, gastrointestinal 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: An increased incidence of hypertension has been observed in patients treated with bevacizumab. 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).

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). 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. NCI-Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio at least every 9 weeks. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

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.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis: In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%).

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

The incidence of NCI-CTCAE Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; no fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure).

In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

Arterial Thromboembotic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

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 and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment 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, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%−1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to $>$ 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

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 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving 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 or 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 weeks and bevacizumab no earlier than 8 weeks after surgery).

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: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC.
Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Mucocutaneus Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTCAE 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.

Reversible Posterior Leukoencephalopathy Syndrome: There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker et al. 2006; Ozcan et al. 2006).

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240–360 mg/m^2). Many of these patients also had prior radiotherapy to the left

chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al. 2005).

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTCAE Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm.

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well (Karp et al. 2004).

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone (Sandler et al. 2006).

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

1.7 OXALIPLATIN

Oxaliplatin is a diaminocyclohexane (DACH)-platinum compound, active in several solid tumor types, including some cisplatin/carboplatin refractory diseases. The mechanism of action of oxaliplatin is similar to that of cisplatin as well as other platinum (Pt) compounds. Oxaliplatin forms intrastrand Pt-DNA adducts/crosslinks between two adjacent or close guanines (GG or GNG) or

adjacent guanine-adenine (GA) base pairs. The formation of these Pt-DNA crosslinks inhibits DNA replication and transcription, resulting in cell death in actively dividing cells. In addition to intrastrand DNA crosslinks, use of oxaliplatin, like other Pt compounds, can result in Pt-DNA interstrand crosslinks. Oxaliplatin can also cause Pt-DNA-protein crosslinks, although to a lesser extent.

Studies indicate that the types and percentages of Pt-DNA adducts formed by oxaliplatin are qualitatively similar to those formed by cisplatin. However, the following preclinical data with oxaliplatin suggest several unique attributes related to the cytotoxic/antitumor activity of oxaliplatin compared to cisplatin:

1) DACH-Pt DNA adducts are bulkier and more hydrophobic than cis-diammine-Pt DNA adducts and may be more effective in DNA synthesis inhibition.

2) DNA mismatch-repair complexes do not recognize DACH-Pt DNA adducts.

3) Experimental data on naked and intracellular DNA suggest that oxaliplatin Pt-DNA adducts have higher cytotoxic efficacy than cisplatin Pt-DNA adducts.

Oxaliplatin demonstrates a broad spectrum of in vitro cytotoxic and in vivo antitumor activity that differs from that of either cisplatin or carboplatin. Oxaliplatin is active against several cisplatin-resistant cell lines, colon carcinoma, and other solid tumors that are not responsive to cisplatin. In addition, oxaliplatin in combination with 5-FU leads to synergistic antiproliferative activity in vitro, as well as in vivo in several tumor models**.**

a. Oxaliplatin Safety Profile

Neurotoxicity is the dose-limiting toxicity of oxaliplatin. The most common acute side effect is a transient peripheral neurotoxicity characterized by paresthesia and dysesthesia in hands, feet and the peri-oral area, triggered and/or enhanced by contact with cold. Some patients report laryngopharyngeal dysesthesia when swallowing cold food or drink. The intensity is generally mild to moderate. These symptoms are often observed during oxaliplatin infusion, lasting for a few minutes to a few days, and are fully reversible. This toxicity, already observed at

doses of 90 mg/m², increases with dose, to affect 75% of patients treated at 200 mg/m².

The incidence and intensity of symptoms increase with the number of cycles, with a median time of evolution to grade 3 of 23 weeks when administered as a single agent at 130 mg/m^2 every 3 weeks.[29] Women seem more likely than men to experience severe neurotoxicity. Interestingly, these symptoms disappear within 3 months of stopping treatment in 50% of patients and in 90% of patients by one year.

At doses higher than 45 mg/m², oxaliplatin induces nausea and vomiting with rapid onset in the majority of patients; this can last for 24 to 48 hours and is generally controlled by the standard anti-emetic measures used for all platinum derivatives. Gastrointestinal toxicity, such as diarrhea, is less common (up to 25% of cycles) and rarely severe.

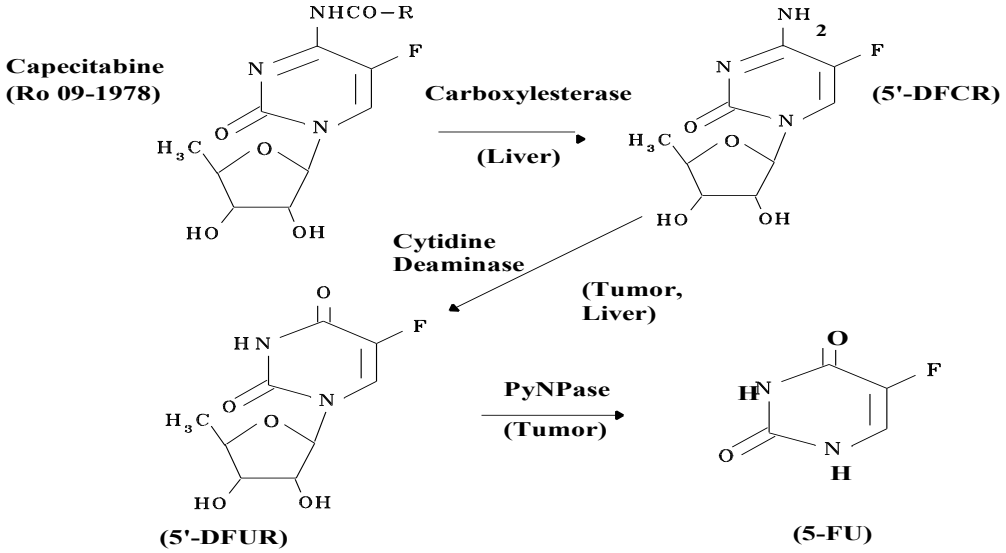
Hematological toxicity is minor and sporadic. In monotherapy studies, 2% of patients experienced grade 3-4 anemia and neutropenia.[29] No grade 3-4 thrombocytopenia occurred, but grade 2 thrombocytopenia was seen in 14%. No significant renal toxicity and ototoxicity were reported with oxaliplatin although no studies were performed which included patients with severe renal impairment. Allergic reactions to oxaliplatin are rare: 1.5% purely cutaneous and <0.5% anaphylactic.

1.8 CAPECITABINE

Capecitabine is an oral fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumor tissue through exploitation of high intratumoral concentrations of thymidine phosphorylase [39;40]. Human pharmacokinetic studies have shown that after oral administration, capecitabine is rapidly and almost completely absorbed through the gastrointestinal wall, thus avoiding direct intestinal exposure to 5-FU. Capecitabine is then metabolized to 5-FU via a three-step enzymatic cascade. After oral administration, capecitabine is absorbed unchanged from the gastrointestinal tract, and is sequentially converted to the cytotoxic moiety, 5-FU in a series of metabolic steps. First, capecitabine is metabolized primarily in the liver by the 60kDa carboxylesterase to 5’-deoxy-5-fluorocytidine (5’-DFCR). 5'-DCFR is then converted to 5’-DFUR by cytidine deaminase, which is principally, located in the liver and tumor tissues

(Figure 2). Metabolism of 5'-DFUR to the pharmacologically active agent 5-fluorouracil (5-FU) occurs preferentially at the tumor site by the tumor-associated angiogenic factor, thymidine phosphorylase (dThdPase). Concentrations of dThdPase are higher in colorectal tumor tissues than in normal tissues, accounting for the preferential activation of 5-FU in tumor.[30]

Figure 2: Metabolism of Capecitabine



a. Capecitabine Safety Profile

The main toxicities of capecitabine included diarrhea, mucositis, and palmar-plantar erythrodysesthesia (hand-foot syndrome). Overall, the clinical safety profile of capecitabine is similar to that of fluoropyrimidines. Important differences however are noted: patients who receive capecitabine experience a lower incidence of grade 3/4 stomatitis and grade 3/4 neutropenia leading to a significantly lower incidence of neutropenic fever and sepsis, a similar incidence of grade 3/4 diarrhea and a higher incidence of grade 3 hand-foot syndrome [41].

Severe myelosuppression is uncommon with capecitabine. Grade 3/4 neutropenia occurred in 2.2% of patients. Neutropenia and neutropenic fever as a serious clinical adverse event occurred at 0.5% and 0.2% of patients, respectively. Sepsis and septicemia as a serious clinical adverse event occurred at 0.2% and 0.2% of patients.

Hyperbilirubinemia was observed. Elevations higher than three times the upper limit of normal (ULN) (grade 4 according to NCI-CTCAE) were reported in 4.5% of patients. The incidence of patients with grade 3 hyperbilirubinemia (elevations higher than 1.5 x ULN) was 18.3%. Grade 3 or 4 hyperbilirubinemia was usually not associated with other signs of liver disturbance. Persistence of hyperbilirubinemia tended to be associated with liver metastases. There was no evidence of a cumulative effect.

The incidence of hospitalization due to treatment-related adverse events was 11.6%. Of these, hospitalizations due to treatment-related events associated with neutropenia (infection, neutropenia, neutropenic fever, and sepsis) were low (incidence of 0.2% per event). Diarrhea led to hospitalization in 4.2% of patients. The incidence of hospitalizations due to dehydration and stomatitis was 2.2% and 0.2%, respectively. Hand-foot syndrome rarely required hospitalization.

Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment treated with capecitabine 1250 mg/m^2 twice-daily (monotherapy), there is no evidence for an effect of creatinine clearance on the pharmacokinetics of intact drug and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5'-DFUR (35% increase in AUC when creatinine clearance decreases by 50%) and to FBAL (114% increase in AUC when creatinine clearance decreases by 50%) [47,48]. 5'-DFUR is the direct precursor of 5-FU, and FBAL is a metabolite without antiproliferative activity.

Analyses of the pharmacokinetic study in cancer patients with mild to severe renal impairment and overall clinical safety data from capecitabine clinical trials [48] indicated that: Patients with severe renal impairment at baseline (calculated creatinine clearance <30 mL/min) had a high rate of grade 3-4 toxicity and serious adverse events and shorter treatment duration and as a consequence capecitabine was contraindicated in this population. Patients with moderate renal impairment at baseline (calculated creatinine clearance 30-50 mL/min) had a greater overall incidence of treatment-related grade 3-4 toxicity and serious

adverse events relative to patients with normal renal function. Patients with mild renal impairment at baseline (calculated creatinine clearance 51-80 mL/min) experienced slightly more serious adverse events and withdrawals due to adverse events than the patients with normal renal function and maintained their overall benefit/risk ratio. As a consequence, careful monitoring during capecitabine treatment is advised.

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine and occurred in patients with and without liver metastases. In a drug interaction study with single dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

1.9 CAPECITABINE PLUS OXALIPLATIN (CAPOX)

An initial phase II study of the combination of oral capecitabine and intravenous oxaliplatin (oral capecitabine 1000 mg/m^2 twice daily days 1-14, intravenous oxaliplatin 130 mg/m^2 day 1) administered every 3 weeks was conducted as first line therapy in metastatic colorectal cancer patients [31]. Ninety-six patients received CAPOX and were assessable. The most frequent related grade 3-4 adverse reactions were sensory neuropathy (14%), diarrhea (14%), nausea/vomiting (13%), asthenia (9%), stomatitis (6%), neutropenia (5%), thrombocytopenia (4%) and hand-foot syndrome (3%). Despite the long treatment duration in this trial (median of 10 cycles of CAPOX or capecitabine alone), approximately half the patients (47%) did not require any dose reductions. Eighteen percent required only capecitabine dose reduction, 14% required only oxaliplatin dose reduction and 22% had a reduction of both agents.

Since this initial phase II trial, a number of studies have utilized the CAPOX regimen in various schedules. A recent large phase III study, NO16966, evaluated CAPOX versus FOLFOX4 in 1401 patients. CAPOX (oxaliplatin 130mg/m^2 IV, capecitabine 1000mg/m^2 BID D1-14 q21d) was administered with or without bevacizumab.[32] Grade 3-4 diarrhea was higher with CAPOX, 20%

vs. 11%, and hand-foot syndrome was higher with CAPOX, 6% vs. 1%. Grade 3/4 neutropenia was markedly lower in the CAPOX arm, 7% vs. 43%.

Tolerance to CAPOX has been demonstrated to relate to geographical location with higher toxicity seen at the same dosing in the United States and Canada versus Europe. A retrospective review of data from treatment with either capecitabine or intravenous 5-FU in 1189 metastatic patients and 1861 adjuvant-treated patients demonstrated that grade 3/4 toxicity was higher in the USA cohort in comparison to the non-USA cohort. This occurred for both capecitabine and intravenous 5-FU.[33] In addition data from the TREE-1 and TREE-2 studies also support a lower capecitabine dose when administered in the United States. The TREE studies were conducted in metastatic colorectal cancer and each study had three arms, CAPOX, FOLFOX or bolus 5-FU with oxaliplatin. In TREE-2 study bevacizumab was added to these three combinations. Due to toxicity in the TREE-1 CAPOX arm with capecitabine at 2000mg/m^2/day the dose was reduced to 1700mg/m^2/day for TREE-2. With this reduction in dose, toxicity decreased, tolerance improved, and activity markedly improved. When comparing CAPOX in TREE-1 vs. TREE-2 grade 3-4 adverse events were: vomiting 19% vs. 7%, dehydration 21% vs. 8%, diarrhea 27% vs. 17%, and neutropenia 21% vs. 8%. While the response rate improved with the addition of bevacizumab in the FOLFOX arm from 41% to 52%, the response rate in the CAPOX arm dramatically improved from 27% to 46%.[34] Thus, in the United States, in general, the standard dose of capecitabine in the CAPOX regimen varies from 750mg/m^2 twice daily to 850mg/m^2 twice daily.

Our recently completed study of CAPOX (oxaliplatin 130mg/m^2 administered intravenously on Day 1 and capecitabine 750mg/m^2 administered orally twice a day on Days 1-14, repeated every 3weeks) in SBA and AAC utilized a well-tolerated capecitabine dose of 750mg/m^2 twice daily. This study demonstrated grade 3-4 non-hematologic toxicity in 29% of patients and grade 3-4 hematologic toxicity in 13%.[15] The most common grade 3-4 non-hematologic toxicity was fatigue, which was observed in 20% of the patients. Grade 3-4 diarrhea was seen in 5% of patients. This well-tolerated dosing of CAPOX will be the equivalent dosing utilized in the study described in this protocol.

Due to safety concerns from the use of an oral chemotherapy medication, patients will be educated to stop capecitabine at the first signs of grade 2 toxicity,

and only to restart with the agreement of the physician, when toxicity has subsided to grade 1 or less.

1.10 CAPOX PLUS BEVACIZUMAB SAFETY PROFILE

A number of studies have evaluated the combination of CAPOX and bevacizumab. In general the addition of bevacizumab to CAPOX results in additional toxicities related to the use of bevacizumab but does not alter the side effect profile of CAPOX. The randomized phase II TREE study compared two successive cohorts of patients. In TREE-1 (n=150) patients were treated with either FOLFOX or bolus 5-FU or CAPOX and in TREE-2 (n=223) patients were treated with the same regiments but also received bevacizumab.[27] Capecitabine dosing in TREE-2 was lower than in TREE-2 with capecitabine reduced from 2000mg/m^2/day to 1700mg/m^2/day. Toxicity with CAPOX/bevacizumab compared to CAPOX was improved with a reduction in grade 3-4 adverse events from 67% to 51%, and in particular a reduction in diarrhea (31% vs. 19%), nausea/vomiting (38% vs. 21%), dehydration (27% vs. 8%), and hand-foot syndrome (21% vs. 10%). Grade 3-4 adverse events that were higher in the bevacizumab treated patients were hypertension (15% vs. 2%) and deep vein thrombosis (3% vs. 0%).

The phase III XELOX-1/NO16966 study, evaluated 1401 patients treated with CAPOX or FOLFOX with or without bevacizumab.[28] Similar rates of grade 3-4 toxicity were seen between the two arms with the placebo arm demonstrating a rate of 15% and the bevacizumab arm demonstrating a rate of 21%. Grade 3-4 adverse events that were higher with bevacizumab were venous thromboembolism (8% vs. 5%), hypertension (4% vs. 1%), bleeding (2% vs. 1%), and arterial thromboembolic events (2% vs. 1%).

1.11 STUDY RATIONALE

Adenocarcinoma of the small bowel is a rare cancer that has many molecular, genetic, and epidemiological similarities with adenocarcinoma of the large bowel. In particular both cancers demonstrate a similar frequency of expression of VEGF-A. The use of anti-VEGF antibodies, such as bevacizumab, has

demonstrated clear anti-cancer activity in the treatment of adenocarcinoma of the colorectum.

Thus, given these known facts, we hypothesize that the addition of bevacizumab to CAPOX chemotherapy will result in improved anti-cancer activity and improved outcomes for patients with metastatic adenocarcinoma of the small bowel and ampulla of Vater. We now propose a study to test this hypothesis by evaluating the addition of bevacizumab to the standard of care chemotherapy treatment, CAPOX, for metastatic SBA and AAC.

2.0 OBJECTIVES

2.1 PRIMARY

- To determine the progression-free survival (PFS) at six months for patients with advanced adenocarcinoma of the small bowel or ampulla of Vater treated with capecitabine, oxaliplatin (CAPOX) and bevacizumab

2.2 SECONDARY

- To determine the response rate (RR) for CAPOX and bevacizumab
- To determine the overall PFS for CAPOX and bevacizumab
- To determine the overall survival (OS) for CAPOX and bevacizumab
- To determine the toxicity of CAPOX and bevacizumab

3.0 STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a single-center open-label single arm phase II study. All patients must be registered on the M. D. Anderson Cancer Center Clinical Oncology Research (CORe) system prior to initiation of treatment.

3.2 OUTCOME MEASURES

3.2.1 Primary Outcome Measure

Progression-free survival at six months is the primary outcome measure.

3.2.2 Secondary Outcome Measures

Response rate as per RECIST 1.1, overall PFS, OS, and safety.

4.0 SAFETY PLAN

See Section 4.1 for complete details of the safety evaluation for this study.

4.1 GENERAL PLAN TO MANAGE SAFETY

a. 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. 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 (28–35 days) after the decision to discontinue treatment (see Section 9).

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 9 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 weeks and bevacizumab no earlier than 8 weeks after surgery).

Please see Section 7.4 for detailed instructions for the management of other study drug–related toxicities.

5.0 STUDY SUBJECTS

5.1 SUBJECT SELECTION

Patients will be included in the study based on the following inclusion and exclusion criteria.

5.2 INCLUSION CRITERIA

- Patients must have histologically confirmed adenocarcinoma of the small bowel or ampulla of Vater.
- Prior adjuvant chemotherapy (including 5-FU, capecitabine, and oxaliplatin) for the treatment of adenocarcinoma of the small bowel or ampulla of Vater is allowed if completed ≥ 52 weeks prior to first dose of study treatment.
- Prior capecitabine or 5-FU administered as a radiosensitizing agent concurrently with external beam radiotherapy is allowed.
- Patients must have metastatic disease
- A minimum of 4 weeks must have elapsed from completion of any prior chemotherapy or radiotherapy or surgery and the start date of study therapy.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 (Appendix 1).
- Adequate organ function including:

Absolute neutrophil count (ANC)	≥1,500/ul
Platelets	≥100,000/ul
Total bilirubin [$]	≤1.5 x ULN

AST (SGOT) and ALT (SGPT)	< 3 x ULN
Calculated # creatinine clearance (CrCL)	> 50 cc/min

$ In patients with known Gilbert's syndrome direct bilirubin ≤1.5 x ULN will be used as organ function criteria, instead of total bilirubin

Calculated creatinine clearance (CrCl) calculated using the Cockcroft and Gault formula (Appendix 2).

- Negative serum or urine pregnancy test in women with childbearing potential (defined as not post-menopausal for 12 months or no previous surgical sterilization), within one week prior to initiation of treatment.
- Patients must sign an Informed Consent and Authorization indicating that they are aware of the investigational nature of this study and the known risks involved.
- The effects of the combination of CAPOX and bevacizumab on the developing fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry, for the duration of study participation, and for six months following the completion of therapy. Should a woman become pregnant while participating in this study, she should inform her treating physician immediately. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with oxaliplatin or capecitabine or bevacizumab, breast feeding must be discontinued.

5.3 EXCLUSION CRITERIA

Subjects meeting any of the following criteria are **ineligible** for study entry:

- Patients who have received prior chemotherapy for their metastatic disease are excluded. Chemotherapy if given as a radiation-sensitizer is allowed.
- Patients may not be receiving any other investigational agents nor have received any investigational drug 28 days prior to enrollment.

- Known history of dihydropyrimidine (DPD) deficiency.
- Peripheral neuropathy of grade 3 or greater by Common Terminology Criteria for Adverse Events (CTCAE) 4.0.
- Gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation.
- Because of the interaction between coumadin and capecitabine, patients taking therapeutic doses of coumarin-derivative anticoagulants, are not eligible. Low-dose Coumadin (e.g. 1 mg PO per day) in patients with in-dwelling venous access devices is allowed but frequent INR monitoring is recommended.
- Prior treatment with bevacizumab or known hypersensitivity to any component of bevacizumab.
- Inadequately controlled hypertension (defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure > 90 mmHg)
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix 5)
- History of myocardial infarction or unstable angina within 6 months prior to Day 1
- History of stroke or transient ischemic attack within 6 months prior to Day 1
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1
- History of hemoptysis ($\geq$ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1
- History of abdominal fistula or gastrointestinal perforation which must have resolved at least 6 months prior to Day 1

- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 or anticipation of need for major surgical procedure during the course of the study.
- Core biopsy or other minor surgical procedure excluding placement of a vascular access device, within 7 days prior to Day 1.
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria at screening as demonstrated by either (1) urine protein:creatinine (UPC) ratio of ≥ 1.0 or (2) urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).
- Known CNS disease, except for treated brain metastasis. Treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Anticonvulsants (stable dose) are allowed. Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 will be excluded
- Current, recent (within 4 weeks of the first infusion of this study), or planned participation in an experimental drug study other than this study
- Pregnancy (positive pregnancy test) or lactation.
- Active malignancy, other than superficial basal cell and superficial squamous (skin) cell, or carcinoma in situ of the cervix, within last five years
- Inability to comply with study and/or follow-up procedures
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, or psychiatric illness/social situations that would limit adherence with study requirements.

- Age <18 years. Because no dosing or adverse event data are currently available on the use of CAPOX and bevacizumab in patients <18 years of age, children are excluded from this study.

6.0 STUDY DESIGN

6.1 TREATMENT PLAN

This is a single-center open-label single arm phase II study. All patients must be registered on the M. D. Anderson Cancer Center Clinical Oncology Research (CORe) system prior to initiation of treatment.

A maximum of thirty patients will be accrued to this study. Accrual is projected to be 1 to 1.5 subjects per month, with accrual completion within 24 months of study activation. The last study visit is projected to be 36 months from study activation.

Treatment will consist of intravenous oxaliplatin administered on Day 1, intravenous bevacizumab administered on Day 1, and oral capecitabine administered twice daily on Days 1-14. A cycle of therapy is defined as 21 days. Restaging will be done every 3 cycles (+/- 1week allowance is made for scheduling). Treatment will be continued until progression unless other reasons for study discontinuation occur as listed in section 9 “Study Discontinuation.”

Table 2: **Starting Dose Level**

Drugs	**Dose**	**Schedule**
Oral Capecitabine:	750 mg/m^2 BID (total daily dose 1500 mg/m^2)	Days 1-14 with first dose to begin the morning or evening of Day 1*
IV Oxaliplatin:	130 mg/m^2	Day 1 over 2 hours (administer prior to bevacizumab)
IV Bevacizumab:	7.5 mg/kg	Day 1 over 90 minutes (if well-tolerated, subsequent infusion time can be decreased to 60 and then 30 minutes)

*On Day 1 of any cycle, the first dose of capecitabine may be administered in the evening. If this occurs, the last dose of capecitabine for the cycle would be taken on the morning of Day 15.

7.0 STUDY MEDICATION

Dose modifications and treatment delays based on observed drug-related toxicity will be performed as described below. A cycle of therapy may be delayed up to 2 weeks to allow for weather events, patient's personal emergencies, observation of holidays, or other unforeseen delays that the Investigator deems to be in the best interest of the patient.

All doses of oxaliplatin and capecitabine will be calculated on the basis of milligrams of each drug per square meter (mg/m^2) of body surface area (BSA). BSA will be recalculated prior to each cycle. Refer to Appendix 3 for the rounded total daily dose of capecitabine in mg each patient should receive. Doses of bevacizumab will be calculated based on the patient's actual body weight in kilograms prior to each cycle.

7.1 BEVACIZUMAB

7.1.1 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 will be supplied in 20-cc (400-mg) glass vials containing 16 mL bevacizumab (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.

7.1.2 Bevacizumab Administration

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. It is not necessary to correct dosing based on ideal weight.

The initial dose will be delivered over 90±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±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±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.

7.1.3 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.

7.1.4 How Supplied

Bevacizumab will be supplied by Genentech. Unused or expired medication will be returned to Genentech.

7.2 OXALIPLATIN

7.2.1 Active Ingredient

Oxaliplatin or Eloxatin® has the chemical name of Trans-/-diaminocyclohexane oxalatoplatinum cis-[oxalato(trans-/-1,2-diaminocyclohexane) platinum(II)].

Oxaliplatin has a molecular weight of 397.3 D. It is slightly soluble in water and an aqueous solution of 2mg/ml has a pH between 4.8 and 5.7.

7.2.2 Finished Product

Oxaliplatin is presented in the form of a white to off-white cake or powder contained in clear glass vials sealed with a rubber stopper and an aluminum seal with a flip-off cover.

Table 3: Oxaliplatin composition

	50 mg vials	100 mg vials
Oxaliplatin	50 mg	100 mg
Lactose monohydrate	450 mg	900 mg
Nominal volume of vial	36 ml	50 ml

7.2.3 Route of Administration

Intravenous

7.2.4 Reconstitution

The freeze-dried powder is reconstituted by adding 10 (for the 50 mg vials) or 20 (for the 100 mg vials) ml of water for injection or 5% dextrose solution and then by diluting in an infusion solution of 250 to 500 ml of 5% dextrose solution. Dispose of any reconstituted solution that shows evidence of precipitation. Always use the recommended solvents. Never administer undiluted solution. Reconstitution or final dilution must never be performed with sodium chloride solution.

Oxaliplatin must be infused by central venous line over 2 hours. If acute (occurring during or after the 2 hour infusion) laryngopharyngeal dysesthesias occur, increase duration of the infusion to 6 hours. Ensure the infusion lines are adequately flushed with 5% dextrose solution between the administration of any other drug. The administration of oxaliplatin does not require pre-hydration.

7.2.5 Incompatibilities/Precautions

Do not mix or administer with saline or other chloride containing solutions. Oxaliplatin is unstable in the presence of chloride. Do not simultaneously administer other drugs by the same infusion line. Do not combine with alkaline solutions. Oxaliplatin is unstable under alkaline conditions. Do not use components containing aluminum (i.e. needles or intravenous sets) for the preparation or administration of oxaliplatin. There is risk of degradation when in contact with aluminum

Flush line after oxaliplatin administration. Flush lines with a 5% dextrose solution after oxaliplatin is given and before administration of supportive care medications.

7.2.6 How Supplied

Commercial drug supply will be used.

7.2.7 Storage and Handling

Unreconstituted vials may be stored for 3 years at room temperature up to 30°C (86°F). Reconstituted solution, in 5% dextrose solution or water for injection and in the original vial, should not be stored for more than 24 hours between 2°C and 8°C. Solution for infusion, after dilution in 250 to 500 ml of 5% dextrose solution, should be used immediately.

All cancer chemotherapeutic agents should be handled with utmost care during preparation and administration. They should not be prepared by pregnant or breast-feeding women or by persons allergic to that agent. To avoid any form of physical contact with the drug by the health care provider, gown, gloves and masks should be worn when appropriate. As a parenteral agent, oxaliplatin should be prepared in a vertical-flow biologic safety cabinet. All equipment used to prepare and administer the drug should be destroyed according to standard

hospital procedures for disposal of cytotoxic waste. Refer to hospital guidelines for any additional precautions that may apply.

7.3 CAPECITABINE

7.3.1 Active Ingredient

Capecitabine is a fluoropyrimidine carbamate. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil via three enzymatic steps carried out by the enzymes, 5'deoxy-5-fluorocytidine, 5'-deoxy-5-fluorouridine, and thymidine phosphorylase.

7.3.2 Finished Product

Capecitabine is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine. For dosing convenience, only the 500 mg tablet will be used in this study.

7.3.3 Route of Administration

Oral

7.3.4 Drug Interactions

A drug interaction between capecitabine and coumarin anticoagulants has been reported. Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine and occurred in patients with and without liver metastases. In a drug interaction study with single dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Antivirals, Sorivudine, also called BV-araU or brovavir or Usevir, or its chemically related analogues, such as brivudine, approved in Europe only, interact with capecitabine. A clinically significant drug-drug interaction between sorivudine

and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase (DPD) by sorivudine, has been described. This interaction leads to increased fluoropyrimidine toxicity and is potentially fatal.

Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms. Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin, suggesting a potential interaction.

7.3.5 How Supplied

Commercial drug supply will be used.

7.3.6 Storage and Handling

Store at 25° C (77°F); excursions permitted to 15° C to 30°C (59° C-86°F), keep tightly closed.

7.4 DOSE MODIFICATIONS AND/OR DELAYS DUE TO TOXICITY

Toxicity will be graded according to the NCI CTCAE, Version 4.0 (which is available at: http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm) except for neurosensory and skin toxicity. Neurosensory toxicity will be graded according to the Neurologic Toxicity Scale for Oxaliplatin Dose Adjustments, Table 5 below. For any CTCAE toxicity thought to be at least possibly related to therapy, further treatment will be guided by the dose adjustment tables 4, 5, and 6.

For any event which is apparent at baseline, the dose modification will apply according to the corresponding shift in toxicity grade if the investigator feels this is appropriate, (e.g. if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of 1 grade and treated as a grade 1 toxicity for dose modification purposes). Neurosensory toxicity does not result in dose reduction for capecitabine or bevacizumab. If creatinine clearance declines to <50 ml/min during the study, no capecitabine dose reduction is required unless there are concomitant AEs requiring reduction.

In patients with known Gilbert's syndrome, direct bilirubin will be used to assess organ function instead of total bilirubin.

Capecitabine treatment interruptions are regarded as lost treatment days and missed doses should not be replaced; the planned treatment schedule should be maintained. Once a dose of capecitabine or oxaliplatin has been reduced, it should not be increased at a later time. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in progress notes. Radiographic tumor evaluation should be performed every 3 cycles. Scheduling flexibility of +/- 1 week is allowed for radiographic imaging. Evaluations earlier than every 3 cycles are allowed if, in the investigator's opinion, this evaluation is in the patient's best interest.

A new cycle of chemotherapy with capecitabine, oxaliplatin, and bevacizumab will be delayed until:

- Absolute neutrophil count ≥ 1000/mm^3 and platelet count ≥ 75,000/mm^3
- Recovery from any treatment-related non-hematological toxicity (except alopecia, and oxaliplatin-related neurosensory toxicity) to baseline or ≤ grade 1. At the treating physician's discretion a new cycle may be started with a grade 2 toxicity, if the toxicity is not felt to be clinically meaningful and is in the best interest of the patient.

If toxicity requires a dosing delay for more than four weeks from the planned cycle, study treatment will be discontinued. If capecitabine or bevacizumab must be discontinued permanently due to toxicity, study treatment will be discontinued. If oxaliplatin must be discontinued permanently due to either neurological toxicity or hypersensitivity reaction, then treatment with capecitabine and bevacizumab may continue on protocol. In addition oxaliplatin may be discontinued permanently for recurrent thrombocytopenia (Grade 3 or Grade 2 thrombocytopenia that is not recovered to grade ≤1 by Day 28) despite two oxaliplatin dose reductions and for persistent fatigue in patients who have been on treatment for over six months. Persistent fatigue is defined as grade 2 or more fatigue on two sequential cycles in a patient who has been on study for greater than six months from the first dose of study drug. If the reason for oxaliplatin discontinuation is due to any other toxicity then study treatment will be discontinued. Two dose reductions are allowed for capecitabine and oxaliplatin (see table 7). If a third reduction is required then that patient will be removed

from the study. If the treating physician feels that the given toxicity requiring dose adjustment is only due to one study drug, oxaliplatin or capecitabine, than dose adjustment for only that one study drug may be done. There are no dose adjustments for bevacizumab. For management of adverse events due to bevacizumab see table 4. For dose modifications due to capecitabine and oxaliplatin see tables 5 and 6.

7.4.1 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. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; 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. 4.0 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 4.

Table 4
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 hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
No dose modifications for grade 1-2 non-pulmonary and non-CNS events	
Grade 3 Non-pulmonary and non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4 non-pulmonary or non-CNS hemorrhage	Discontinue bevacizumab.
Grade 1pulmonary or CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary or CNS hemorrhage	Discontinue bevacizumab
Venous Thrombosis	
No dose modifications for grade 1-2 events	

Table 4

Bevacizumab Dose Management due to Adverse Events (continued)

Grade 3 or 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Arterial Thromboembolic event (New onset, worsening, or unstable 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 No dose modifications for grade 1-2 events	
Grade 3 (UPC> 3.5, urine collection > 3.5 g/24 hr)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ratio ≤ 3.5 or 24 hr collection ≤ 3.5 g
Grade 4 (nephritic syndrome)	Discontinue bevacizumab
GI Perforation	Discontinue bevacizumab.
Fistula	
Any grade (TE fistula)	Discontinue bevacizumab.
Grade 4 fistula	Discontinue bevacizumab.
Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.

Table 4

Bevacizumab Dose Management due to Adverse Events (continued)

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 Any grade (requiring medical or surgical therapy)	**Discontinue bevacizumab.**
Reversible Posterior Leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to ≤ Grade 1
Grade 4	Discontinue bevacizumab.

7.4.2 Oxaliplatin and Capecitabine Dose Modification and Toxicity Management

Table 5: Dose Modifications

	During a Cycle	**Start of New Cycle**	
	Dose Adjustments During a Cycle of Therapy	**Dose Adjustments at the Start of Subsequent Cycles of Therapy (Change from previous cycle's starting dose based upon maximum toxicity encountered in the previous cycle)**	
NCI CTCAE Toxicity Grade	Capecitabine	Capecitabine	Oxaliplatin
Hematological Toxicity (except anemia)*			
1 or 2	Maintain dose	Maintain dose	Maintain dose
3 or 4	Interrupt until grade 0-1, then continue with unchanged dose	Maintain dose	Reduce one dose level
Febrile neutropenia (grade 3 or 4)	Interrupt until clinical resolution, in the investigator's opinion, then dose reduce by one dose level.	Reduce one dose level	Reduce one dose level
Grade 2 thrombocytopenia not recovered to ≤grade 1 by Day 28		Maintain dose	Upon recovery, treat at one dose level reduction
Non-Hematological Toxicity except for Acute Hyersensitivity Reaction, Hand-Foot Syndrome, Grade 2 Nausea/Vomiting, and Nail/Skin toxicities. For neurological toxicities, see Table 6.			
1	Maintain dose	Maintain dose	Maintain dose
2	Interrupt until resolved to grade 0-1 (grade 0/baseline for diarrhea/cramps), then continue at 100% of dose. If grade 2 toxicity recurs, continue at same dose, or at the discretion of the investigator, one dose level reduction.	Treat at 100% of dose, or at the discretion of the investigator, reduce one dose level	Maintain dose
3	Interrupt until resolved to grade 0- 1 (grade 0/baseline for diarrhea/cramps), then continue one dose level reduction	Reduce one dose level	Reduce one dose level
4	Interrupt until resolved to grade 0- 1 (grade 0/baseline for diarrhea/cramps), then continue at one dose level reduction. If it recurs, discontinue treatment	Reduce one dose level	Reduce one dose level
Not recovered to baseline or Grade 1 by Day 28		Upon recovery, treat at one dose level reduction	Upon recovery, treat at one dose level reduction

Grade 2 nausea and/or vomiting	Maintain dose #	Maintain dose#	Maintain dose#
Acute Hypersensitivity Reaction Grade 3 or 4	Discontinue treatment**		
Hand-Foot Syndrome: Grade 1 Grade 2 Grade 3 (Grade 4 NA)	 Maintain dose Interrupt until grade 0-1, then continue at one dose level reduction Interrupt until grade 0-1, then continue at one dose level reduction	 Maintain dose Treat at one dose level reduction Treat at one dose level reduction	 Maintain dose For all grades

Two dose reductions are allowed for oxaliplatin and capecitabine. Any patient requiring a third dose reduction will be removed from the study.

* No dose reductions or interruptions will be required for anemia as it can be satisfactorily managed with transfusions and/or erythropoietin.

\# While providing standard medical supportive care for nausea/vomiting

**For grade 3 toxicity treatment may be continued if it is felt to be in the patient's best interest and the treating physician feels the use of additional premedications are likely to eliminate or reduce the severity of the reaction.

Table 6: Neurological Toxicity Scale and Oxaliplatin Dose Adjustments

Toxicity (Grade)	**Duration of Toxicity**		**Persistent between Cycles[a]**
	1-7 days	**>7 days**	
Grade 1 Paresthesias/dysesthesias[b] that do not interfere with function	No change	No change	No change
Grade 2 Paresthesias/dysesthesias[b] interfering with function but not activities of daily living (ADL)[d]	No change	No change	Decrease by one dose level
Grade 3 Paresthesias/dysesthesias[b] with pain or with functional impairment that also interfere with ADL	No change	Decrease by one dose level	Stop oxaliplatin
Grade 4 Persistent paresthesias/dysesthesias[b] that are disabling or life-threatening	Stop oxaliplatin	Stop oxaliplatin	Stop oxaliplatin
Acute laryngopharyngeal dysesthesias[b] (during or after the 2 hour infusion)	Increase duration of next infusion to 6 hours[c]		

a Not resolved at the beginning of the next cycle
b May be cold-induced
c May also be pre-treated with benzodiazepines
d If patient had baseline grade 2 paresthesias/dysesthesias then maintain dose for grade 2 toxicity

Table 7: Dose Levels

	Capecitabine	**Oxaliplatin**	**Bevacizumab**
Dose Level 0	1500 mg/m^2	130 mg/m^2	7.5 mg/kg
Dose Level -1	1125 mg/m^2	97.5 mg/m^2	7.5 mg/kg
Dose Level -2	843 mg/m^2	73 mg/m^2	7.5 mg/kg

7.4.3 Special Instructions Regarding Treatment of Chemotherapy-related Toxicity

Diarrhea

Capecitabine should be stopped at diarrhea ≥ grade 2, and treated symptomatically. The recommended dosage regimen for loperamide: 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Note: This dosage regimen exceeds the usual dosage recommendations for loperamide. Pre-medication with loperamide is not recommended. If control takes longer than 2 days, medical evaluation including relevant diagnostic procedures, alternative treatment and possible investigation of DPD deficiency should be considered. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use. Capecitabine can not be re-started until diarrhea has resolved to grade 0 or baseline.

Nausea/Vomiting >1 Grade

For nausea and vomiting, patients must be supplied with antiemetics (compazine is recommended, 5-HT3 antagonist administration is at the discretion of the investigator). Adequate secondary prophylactic treatment should be initiated once nausea or vomiting has occurred.

Neutropenic Infection

Capecitabine should be stopped immediately. Appropriate anti-infective therapy should be initiated. When the ANC has recovered to ≥1,500/mm3 and the fever or infection has resolved, the patient may restart treatment.

Grade 2/3 Hand-Foot Skin Reaction

Treat symptomatically (emollients are recommended).

Laryngopharyngeal dysesthesias

A loss of sensation of breathing (acute respiratory distress) without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm), also has been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold. Should a patient develop laryngopharyngeal dysesthesia, the

patient's oxygen saturation will be evaluated via a pulse oximeter and, if normal, an anxiolytic agent or benzodiazepine should be given and the patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at 1/3 the rate. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 6-hour infusions (instead of the normal 2-hour infusion). Patients will be counseled to avoid cold drinks and exposure to cold water or air, especially for 3-5 days following oxaliplatin administration.

Oral cryotherapy

Patients on oxaliplatin should not receive oral cryotherapy (such as ice chips) on Day 1 of each cycle as this may exacerbate oral or throat dysesthesias, and laryngopharyngeal dysesthesia.

Allergic reactions

For Grade 1 or 2 acute hypersensitivity reactions, no dose modification is required. Administration of anti-histamine agents and/or steroids should be done according to the institutional policy and the treating physician's judgment. For Grade 3* or 4 acute hypersensitivity reactions, treatment should be discontinued.; *for a grade 3 Oxaliplatin hypersensitivity reaction, treatment may be continued if it is felt to be in the patient's best interest and the treating physician feels the use of additional premedications are likely to eliminate or reduce the severity of the reaction.

Treatment of Oxaliplatin allergic reaction

For Grade 1 or 2 or 3 [after discussion with treating physician for grade3] hypersensitivity reactions the infusions should be stopped until resolution and the administration of an anti-histamine agent and/or steroid is recommended. Upon resolution of symptoms, treatment may resume and a 50% reduction in the rate of infusion should be considered.

Following a Grade 1 or 2 or 3 [after discussion with treating physician for grade 3] hypersensitivity reaction subsequent treatment cycles with oxaliplatin should have additional premedications. Suggested premedications included dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30 minutes

prior to study drug administration. If a Grade 1 or 2 or 3 hypersensitivity reaction persists into the next cycle and it is felt, in the Investigators opinion, it is in the patient's best interest to continue than pre-medication with 50 mg dexamethasone PO 12 hours and 6 hours prior to administration of oxaliplatin can be considered.

Treatment of Bevacizumab allergic reaction

Hypersensitivity reactions to bevacizumab are rare, with severe allergic reactions occuring in 1% of patients. Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a 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.

Pulmonary Fibrosis

In the case of unexplained respiratory symptoms such as nonproductive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further investigations exclude interstitial pulmonary fibrosis.

7.5 BEVACIZUMAB PLUS CAPOX

7.5.1 Capecitabine

Capecitabine will be administered orally as twice-daily intermittent therapy on Days 1-14, followed by 7 days without treatment. The morning and evening dose should be taken approximately 12 hours apart. On Day 1 of any cycle, the first dose of capecitabine may be administered in the evening. If this occurs, the last dose of capecitabine for the cycle would be taken on the morning of Day 15. Capecitabine should be taken with approximately 200 ml of water (not fruit

juices), within 30 minutes after the ingestion of food to improve bioavailability. If the two daily doses are unequivalent, the larger dose should be taken in the evening. Higher levels of thymidine phosphorylase are noted to occur at night and this may improve cytotoxicity. Refer to Appendix 3 for the rounded total daily dose of capecitabine in mg each patient should receive.

7.5.2Oxaliplatin

Oxaliplatin will be administered before bevacizumab at 130mg/m^2 given as a 2-hour intravenous infusion by central venous catheter on Day 1 of a three-week cycle.

7.5.3 Bevacizumab

Bevacizumab will be administered after oxaliplatin at 7.5 mg/kg. The initial dose will be delivered over 90±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±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±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.

7.6 CONCOMITANT MEDICATIONS

Patients are allowed to continue other medications as directed. Any new medications prescribed by other providers or non-prescription medications obtained by the patient shall be reported to the Principal Investigator and noted in the patient's medical record.

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 4, Bevacizumab Dose Management Due To Adverse Events.

Not Permitted

- Any other chemotherapy.
- Prevention of alopecia with cold cap or stomatitis with iced mouth rinses is not permitted (risk of triggering cold-related dysesthesias).
- Concomitant radiotherapy, unless local for control of bone pain, the irradiated area should be as small as possible and lesions within the irradiated field cannot be used for response assessment.
- Capecitabine should not be administered together with sorivudine (antiviral). A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase (DPD) by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.
- Any "herbal" medications or dietary supplements at the discretion of the Investigator.
- Therapeutic anticoagulant dosing of coumarin anticoagulants is not allowed. Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Low-dose Coumadin (e.g. 1 mg PO per day) in patients with in-dwelling venous access devices is allowed but frequent INR monitoring is recommended.

Permitted

- Palliative and supportive care for disease-related symptoms will be offered as needed to all patients in this study.
- Colony-stimulating factors (i.e., G- or GM-CSF) may be used at the discretion of the Investigator..
- Patients taking therapeutic dose-levels of coumarin-derivate anticoagulants concomitantly with capecitabine should be switched to low molecular weight heparin. Low-dose coumadin (e.g. 1 mg po per day) in patients with in-

dwelling venous access devices is allowed but frequent INR monitoring is recommended.

- Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin, suggesting a potential interaction. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored (e.g. weekly phenytoin and albumin levels) for increased phenytoin plasma concentrations and associated clinical symptoms.

8.0 CLINICAL AND LABORATORY EVALUATIONS

Table 8

Evaluation or Procedure	Screening[1]	Study Treatment	End of Treatment Evaluation[12]	30-day Post-Treatment Evaluation[13]/Long Term Follow-up
		On or before Day 1 of each cycle		
Informed consent	X			
Medical History	X			
Physical Examination	X	X[3,4]	X	
Neurosensory assessment [15]	X	X	X	
Inclusion/Exclusion criteria	X			
Height	X			
Weight	X	X[3,4]	X	
Vital Signs (Blood Pressure)	X	X[3,4]	X	
ECOG Performance Status	X	X [3,4]	X	
Hematology[11]	X	X[3,4]	X	
Biochemistry[10,11]	X	X[3,4]	X	
Urine protein:creatinine ratio or urine dipstick for protein[11]	X	Every 3 cycles[14]		
Serum or urine pregnancy test (for females of child-bearing potential)	X			
Optional Collection of Archival Tumor Tissue for Future Research	X[2]			
Toxicity assessment	X	X[3.4]	X	X[8]
Diagnostic Imaging for Tumor Assessment[7]	X	Restaging 3 cycles[5]	X	X[6]
Survival				X[9]

1. Informed consent must be obtained before any evaluations are initiated. Diagnostic imaging studies must be completed within 28 days prior to first day of study treatment. All other baseline evaluations must be completed within 7 days prior to first doses of study drugs.
2. In consenting patients, archival tissue will be collected and stored in a locked cabinet in a locked secure office (FC10.2052) under the direction of the PI for banking for use in future research. The receipt of the archival tissue may take place at any time during the study.
3. For Cycle 1, baseline evaluations will suffice as they are performed within 7 days prior to first dose of study drug (except for imaging studies which are performed within 28 days prior).
4. Within 72 hours prior to start of the cycle (except for Cycle 1 as noted above).
5. Imaging should be obtained every 3 cycles (+/- 1week allowance is made for scheduling). After a tumor demonstrates a tumor response (partial or complete), confirmation of the response will be obtained by a second evaluation to be performed 2 cycles later (+/- 1week).
6. For patients discontinued from the study for reasons other than progression, perform every 12 weeks (+/- 1 week) after the End of Treatment Evaluation visit until documentation of progression or for 12 months after their first dose of study drug, whichever comes first, if no other anti-cancer treatment is given.
7. CT of the chest, abdomen, and pelvis. MRI may be used in cases where it is felt to be unsafe to perform CT secondary to patient's history of dye allergy, or if the tumor is not adequately seen on CT for the purposes of this study.

8. Treatment-related adverse events occurring during study treatment or within 30 days (window of 28-35 days allowed) after the last administration of study drug(s) will be followed until resolution or stabilization. If the patient is unable or unwilling to return to M. D. Anderson for this assessment, the patient will be contacted by phone for this assessment.
9. Every 3 months (+/- 2 weeks) from Post-Treatment Evaluation.
10. Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine, suggesting a potential interaction. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored (e.g. weekly phenytoin and albumin levels) for increased phenytoin plasma concentrations and associated clinical symptoms. Elevations in INR have been correlated with capecitabine and concomitant use of coumadin. Patients taking low dose 1 mg/day of coumadin should receive frequent INR monitoring. The recommended testing frequency is once a week for the first cycle and then on Day 1 of all subsequent cycles.
11. Hematology: hemoglobin, platelets, and absolute neutrophil count. Chemistry: creatinine, total bilirubin, AST, ALT, magnesium, potassium. In patients with known Gilbert's syndrome direct bilirubin will also be performed. Urine protein:creatinine ratio or urine dipstick for protein. Patients discovered to have either a (1) urine protein:creatinine (UPC) ratio of ≥ 1.0 or (2) ≥2+ proteinuria on dipstick urinalysis must undergo a 24 hour urine collection).Creatinine clearance using the Cockcroft and Gault formula should be calculated at baseline and then repeated during the study when deemed necessary by the treating physician.
12. Within 10 days of decision to discontinue study treatment.
13. At 28-45 days from last dose of study medication.
14. +/- 1week allowance
15. As oxaliplatin chemotherapy is neurotoxic a neurosensory assessment should be conducted and grading of this toxicity should be based upon the "Neurologic Toxicity Scale for Oxaliplatin" (table 6)

8.1 PRE-TREATMENT EVALUATIONS

Diagnostic imaging studies (CT scan or MRI of the chest, abdomen, and pelvis) must be completed within 28 days prior to first dose of study drug.

All other baseline evaluations must be completed within 7 days prior to first dose of study drug:

- Medical History
- Neurosensory assessment
- Physical Examination
- Height and weight
- ECOG Performance Status.
- Hematology: hemoglobin, platelets and absolute neutrophil count

- Biochemistry: creatinine (calculate clearance using Cockcroft and Gault formula), total bilirubin (in patients with known Gilbert's syndrome direct bilirubin will also be performed) AST, ALT, magnesium, potassium
- Urine protein:creatinine ratio or urine dipstick for protein. Patients discovered to have either a (1) urine protein:creatinine (UPC) ratio of ≥ 1.0 or (2) ≥2+ proteinuria on dipstick urinalysis must undergo a 24 hour urine collection).
- Serum Pregnancy test for females of childbearing potential
- Toxicity assessment
- Vital signs (blood pressure)

8.1.1 Optional Collection of Tumor Tissue for Future Research:

All patients who sign consent for this study will also be asked to consider participation in this optional part of the study. This collected tissue will be used for future research, at such time as funds are available, to try and further understand the biology of adenocarcinoma of the small bowel and ampulla of Vater. This research will not be undertaken until a laboratory protocol appropriate to the aims of the research has been submitted and received full IRB approval.

In consenting patients, five unstained slides of 5 to 10 microns thick will be requested from the outside institution or prepared from the patient's tumor block, if applicable. The tissue will be stored at MD Anderson Cancer Center in a locked cabinet in a locked, secure office (FC10.2052) under the direction of the PI.

Any residual tumor tissue above what is specified here will be returned to the sending institution.

8.2 EVALUATIONS DURING TREATMENT

Before each cycle (Up to 72 hours prior except for Cycle 1 as noted on Table 8)

- Physical examination
- Neurosensory assessment
- Weight
- ECOG Performance Status
- Hematology: hemoglobin, platelets and absolute neutrophil count
- Vital signs (blood pressure)
- Biochemistry: creatinine (if indicated, calculate clearance using Cockcroft and Gault formula), total bilirubin (in patients with known Gilbert's syndrome direct bilirubin will also be performed), AST, ALT, magnesium, potassium
- Toxicity assessment.

Every 3 cycles (+/- 1 week)

1. Urine protein:creatinine ratio or urine dipstick and 24 hour urine collection if indicated. Patients discovered to have either a (1) urine protein:creatinine (UPC) ratio of ≥ 1.0 or (2) ≥2+ proteinuria on dipstick urinalysis should undergo a 24 hour urine collection.

- CT scan or MRI of the chest, abdomen, and pelvis
- Tumor evaluations will be performed to assess disease response. The same measuring instrument should be used throughout treatment to maintain consistency. After a tumor evaluation is performed which demonstrates a tumor response (partial or complete), confirmation of the response will be obtained by a second evaluation to be performed 2 cycles later.

8.3 END OF TREATMENT EVALUATIONS

Within 10 days of decision to discontinue treatment

- The investigator will evaluate the results of the following clinical and laboratory assessments to be conducted at the time the patient discontinues study treatment:
- Physical examination
- Neurosensory assessment
- ECOG Performance Status
- Weight
- Vital signs (blood pressure)
- Hematology: hemoglobin, platelets and absolute neutrophil count
- Biochemistry: creatinine (if indicated, calculate clearance using Cockcroft and Gault formula), total bilirubin (in patients with known Gilbert's syndrome direct bilirubin will also be performed), ALT, AST, magnesium, potassium.
- Toxicity (adverse events) assessment (including neurologic toxicities)
- Tumor evaluations including CT scan or MRI of the chest, abdomen, and pelvis

8.4 FOLLOW-UP (OFF-TREATMENT)

Follow-up/observation for all treatment related adverse events will be through Day 30 (Day 28 to Day 45 allowed) following the last dose of study drug or until resolution or stabilization of the toxicity or start of another treatment regimen. If it is not feasible for the patient to return to M. D. Anderson for the Day 30 toxicity assessment, the patient will be contacted by phone for this assessment.

Patients with documented (radiological) disease progression at any point during the study will discontinue treatment with study drugs under this protocol. Objective evidence of progressive disease will be recorded at the time of progression. Patients without evidence of progression while on study, regardless of the number of treatment cycles received, will be followed for progression until it is documented. If a patient is off treatment with no documented disease progression and no subsequent anti-cancer treatment is received, he/she should

be followed every 12 weeks (+/- 1 week) after the End of Treatment Evaluation visit with tumor evaluations until disease progression is documented or for 12 months after their first dose of study drug, whichever comes first.

All patients will be followed for survival status every 3 months from End of Treatment evaluation. Survival status may be obtained by checking the electronic medical record or by telephone call.

9.0 SUBJECT DISCONTINUATION

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Treatment delay more than 4 weeks due to toxic effects of study treatment
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Grade 4 hypertension or Grade 3 hypertension not controlled with medication
- 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
- Tracheoesophageal fistula (any grade) or Grade 4 fistula
- Grade ≥ 2 bowel obstruction that has not fully recovered despite medical or surgical intervention
- Wound dehiscence requiring medical or surgical intervention

- Unwillingness or 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 study drug-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.

10.0 RESPONSE EVALUATION

10.1 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international RECIST criteria (version 1.1, 2009) proposed by the RECIST committee. [35] All patients who have measurable disease according to the RECIST criteria and who have their disease re-evaluated will be evaluable for response. For the purposes of this study, patients should be reevaluated for response approximately every 3 cycles. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

10.2 DEFINITIONS

All sites of disease should be followed as either target or nontarget lesions, as categorized at baseline. All measurable lesions up to a maximum of 2 lesions per organ or 5 lesions in total, representative of all involved organs should be identified as target lesions, while all other lesions (either additional measurable lesions or nonmeasurable lesions) should be classified as nontarget lesions. In cases where a target lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. To ensure comparability, the baseline radiology/scans and subsequent radiology/scans to assess response should be performed using identical techniques (eg, scans performed immediately following bolus contrast administration should be made with a standard volume of contrast, the identical contrast agent, and preferably the same scanner). The same method, radiological or physical, should be

employed and assessed by the same individual on each occasion, when possible.

10.3 MEASURABLE DISEASE

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm with CT scan (with minimum slice thickness no greater than 5mm, or 10mm caliper measurement by clinical exam, or 20mm by chest X-ray. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Pathological lymph nodes may also be considered as target or nontarget lesions. To be considered pathologically enlarged and measurable (target lesion), a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). Lymph nodes with a short axis ≥ 10 mm but < 15 mm should be considered nontarget lesions. Lymph nodes that have a short axis < 10 mm are considered nonpathologic and should not be recorded. The short axis measurement of any lymph node that is considered a target lesion should continue to be recorded regardless if the node progresses to below 10 mm. This may prevent the sum of lesions from being zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In rare circumstances, when a target lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

10.4 NON-MEASURABLE DISEASE

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI). For bone and cystic lesions please refer to the RECIST criteria (version 1.1, 2009).

10.5 TARGET LESIONS

All measurable 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 recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters for all target lesions (longest for non-nodal lesions, short axis for nodal lesions) will be calculated and reported as the baseline sum diameters (LD). The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

10.6 NON-TARGET LESIONS

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.7 GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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 is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and Magnetic Resonance Imaging. Conventional CT and MRI should be performed to obtain images of 5 mm or less slice thickness.

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

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.8 RESPONSE CRITERIA

10.8.1 Evaluation of target lesions

- Complete Response (CR): Disappearance of all target and nontarget lesions including normalization of elevated tumor marker level. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm. All nontarget lymph nodes must be nonpathological in size (< 10 mm short axis). Complete response must be confirmed at a second tumor assessment not less than 4 weeks apart from the assessment at which CR was observed.
- Partial Response (PR): At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD. Partial response must be confirmed at a second tumor assessment not less than 4 weeks apart from the assessment at which PR was observed.

- Progressive Disease (PD): At least a 20% increase (and an absolute increase of at least 5 mm) in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute PD. In exceptional circumstances, unequivocal progression of nontarget lesions may be accepted as evidence of disease progression.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
- Non-CR/Non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

10.8.2 Evaluation of non-target lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level
- Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
- Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
- Although a clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the study chair.
- Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

10.9 TIME POINT EVALUATION

At each protocol specified time point, a response assessment occurs. Table 9 provides a summary of this for patients who have measurable disease at

baseline. Table 10 provides a summary of this for patients with non-measurable (therefore non-target) disease.

Table 9: Response for measurable disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	CR	No	CR	≥ 4 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks Confirmation
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least once ≥ 6 weeks from baseline
Not All Evaluated	Non-PD	No	NE	NE
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression. NE = inevaluable Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 10: Response for non-measurable disease

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

NE = inevaluable a ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

10.10 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 11: Response Assignment

Overall Response First Time Point	**Overall Response Subsequent Time Point**	**BEST Overall Response**
CR	CR	CR
CR	PR	SD, PD, or PRa
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

NE = inevaluable a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

10.11 CONFIRMATION

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessment at a minimum follow-up interval of 6 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

10.12 DURATION OF OVERALL RESPONSE

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

10.13 DURATION OF STABLE DISEASE

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.0 STUDY DISCONTINUATION

This study may be discontinued at any time. Reasons for discontinuing the study include but are not limited to the incidence or severity of adverse events observed in this study indicate a potential health hazard to subjects.

12.0 STATISTICAL METHODS

12.1 STUDY DESIGN AND SAMPLE SIZE

This study is a phase II single treatment arm study. Thirty patients will be accrued in this study in total. This sample size will ensure that, if the trial is not terminated early, a posterior 90% credible interval (CI) of PFS at six months will be (0.52, 0.79), assuming that the PFS at 6 months is 0.67 (20/30) with the new treatment.

12.2 PLANNED EFFICACY EVALUATIONS

Endpoint:

The primary endpoint of this phase II, single arm study is progression-free survival (PFS) at 6 months for patients treated with CAPOX plus bevacizumab. PFS is defined as from date of treatment start to date of first documentation of progression or symptomatic deterioration or death due to any cause. Patients last known to be alive and progression free are censored at date of last contact.

Interim Analysis:

A Bayesian sequential monitoring design (Thall et al. 1995) will be used to monitor the trial. Let p1 be the PFS at 6 months of the new treatment and p0 the PFS from the historical data. A previous study with 25 patients with CAPOX alone has shown that PFS at six months is 52%. The prior distributions of p1 and p0 are assumed to be beta(1, 1) and beta(13, 12), respectively. We will stop the trial if Prob{p1 > p0 + 0.15 | data} < 0.025. Following this rule, the trial will be terminated if [# Progression-free]/[# patients evaluated] =< 3/10 and 7/20. In particular, 10 patients will be accrued in the first stage. If 3 or less patients have a PFS over 6 months to the combination treatment, stop the trial and the treatment will be declared as ineffective. If 4 or more patients have a PFS over 6 months, additional 10 patients will be entered in the study with a net total 20 patients in the second stage. If 7 or fewer patients of those 20 patients have PFS over 6 months to the combination treatment stop the trial. If there are 8 or more

patients with PFS over 6 months, additional 10 patients will be entered in the study to reach a total of 30 patients. Accrual will not be suspended for this monitoring; data are analyzed as they accrue.

The operating characteristics based on 1000 simulations are shown in the following table.

Table 12	Stop if Prob{p1 > p0 + 0.15 | data} < 0.025	
True response rate	Pr(stop early)	mean number of patients (median)
0.35	0.69	18 (10)
0.40	0.52	21 (20)
0.50	0.23	26 (30)
0.55	0.13	28 (30)
0.60	0.06	29 (30)
0.65	0.03	30 (30)
0.70	0.01	30 (30)

The probability of treatment related toxicity (grade 3 or 4) will be monitored based on the Bayesian model (beta-binomial) by assuming a priori probability of toxicity following Beta(1,1). The trial will be terminated if Prob(toxicity > 0.25 | data) > 0.8. Following this rule, the trial will be terminated if [# toxicities]/[# patients evaluated] >= 4/10, 5/15, 7/20, and 8/25.

12.3 STATISTICAL ANALYSIS:

Descriptive statistical analysis will be calculated, including histograms or box-plots, proportions, range, means and standard deviations. Fisher's exact test and Wilcoxon rank test will be used in univariate analyses of categorical and continuous variables, respectively. Survival or times to progression functions will be estimated using the Kaplan-Meier method. The two-sided log-rank test will be used to assess the differences of time to events between groups.

Patients who drop out of the study will be included in the time to event data analysis (survival analysis and progression-free survival) as "censored data". For

progression-free survival as a binary endpoint, the intent-to-treat analysis will be performed using all available patients.

13. DATA AND PROTOCOL MANAGEMENT

Data Collection for Enrolled patients

Designated research personnel must enter the information required by the protocol onto electronic Case Report Forms (CRFs). The University of Texas M D Anderson Cancer Center's Clinical oncology Research (CORE) system, and the University of Texas MD Anderson Cancer Center's Protocol Data Management System©(PDMS) CRF system will be used for this study. PDMS is a clinical research information management system. The PDMS CRF is an electronic document designed to record all the protocol-required information to be reported on each trial subject.

PDMS provides data entry templates as defined in the protocol. Laboratory results are automatically transferred from M. D. Anderson Cancer Center Laboratory Medicine's server to PDMS each morning. Users must have clearance through the M. D. Anderson Cancer Center Information Services Security Department in order to access PDMS. PDMS login is password protected.

Only adverse events that are grade 1, 2,3,4,5 possible, probable or definite will be recorded.The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

14. OPTIONAL TISSUE COLLECTION FOR FUTURE RESEARCH

At the time of initial enrollment, patients will be asked to consider consenting to collection of samples of their archival tumor tissue. This optional part of the study will store 5 unstained tumor slides on each consenting patient at MD Anderson Cancer Center for future research purposes. This collected tissue will be used for future research, at such time as funds are available. This research will not be undertaken until a laboratory protocol appropriate to the aims of the research has been submitted and received full IRB approval

All unstained tumor will be stored in a locked cabinet in a locked secure office (FC10.2052) under the direction of the PI. Slides will be de-identified from any personal information and will be labeled by protocol number and patient enrollment number.

15.0 SAFETY REPORTING OF ADVERSE EVENTS

15.1 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.

15.2 REPORTING OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS

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

Genentech Drug Safety
Fax: (650) 225-4682 or (650) 225-5288

(Please use the safety reporting fax cover sheet attached to this document for fax transmission)

STEAES will also be reported to the M. D. Anderson Cancer Center Institutional Review Board as per their requirements.

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.

15.3 Safety Reporting Requirements for IND Exempt Studies

For **Investigator Sponsored IND Exempt Studies**, there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

Postmarketing 15-Day "Alert Report":
The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is **unexpected and assessed by the investigator to be possibly related to the use of Bevacizumab**. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be submitted to the FDA (2 copies) at the following address: Central Document Room, 12229 Wilkins Avenue, Rockville, MD 20852.

All Postmarketing 15-Day "Alert Reports" submitted to the FDA by the Sponsor-Investigator must also be faxed to: Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-5288 (Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

For questions related to safety reporting, contact:

Genentech Drug Safety

Tel: 1-888-835-2555
or
Fax: (650) 225-4682 or (650) 225-5288
(Please use the safety reporting fax cover sheet attached to this document for fax transmission)

16.0 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study, including CRFs, consent forms, laboratory test results, documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be retained by the Principal Investigator for at least 2 years after the investigation is completed.

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Appendix 1

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 2
Calculated creatinine clearance (CrCl) calculated using the Cockcroft and Gault formula

Cockcroft-Gault Formula for Females

Creatinine clearance (mL/min) =
[(140 - age) x weight (in kg) x 0.85] / [72 x serum creatinine (in mg/dL)]

or

[(140 - age) x weight (in kg) x 0.85] / [0.81 x serum creatinine (in µmol/L)]

Cockcroft-Gault Formula for Males

Creatinine clearance (mL/min) =
[(140 - age) x weight (in kg)] / [72 x serum creatinine (in mg/dL)]

or

[(140 - age) x weight (in kg)] / [0.81 x serum creatinine (in µmol/L)]

Appendix 3

Capecitabine Dosing

Doses of capecitabine will be calculated on the basis of milligrams per square meter of body surface area (BSA) (mg/m2). BSA will be recalculated prior to each cycle. **The total daily dose will be administered in 2 divided doses (AM and PM)**. Doses will be rounded as outlined below. Please refer to section 6.0 of the protocol to determine the appropriate mg/m2 dose of capecitabine for each patient.

Calculated **TOTAL Daily Dose** in mg	Actual Rounded Total Daily Dose (this dose is **divided into 2** for a morning and evening dose)	Number of 500 mg tablets to be taken in the **Morning**	Number of 500 mg tablets to be taken in the **Evening**
751-1250 mg	1000 mg	1	1
1251-1750 mg	1500 mg	1	2
1751-2250 mg	2000 mg	2	2
2251-2750 mg	2500 mg	2	3
2751-3250 mg	3000 mg	3	3
3251-3750 mg	3500 mg	3	4
3751-4250 mg	4000 mg	4	4
4251-4750 mg	4500 mg	4	5
4751-5250 mg	5000 mg	5	5

Example:

1. Planned dose of capecitabine to be administered is 1500 mg/m^2/day
2. Patient's BSA is 1.67.
3. Therefore, the **total daily dose** to be administered is 2505 mg.
4. Per the above table, total daily dose is rounded to 2500 mg/day. This will be divided in to a morning and evening dose.
5. The patient will receive two 500 mg tablet in the morning and three 500 mg tablets in the evening.

APPENDIX 4: FDA MEDWATCH 3500a FORM

Form Approved: OMB No. 09 10-0291, Expires 12/31/11
See OMB statement on reverse.

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (1/09)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of ____

Mfr Report #
UF/Importer Report #
FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
In confidence	or ____	☐ Female ☐ Male	____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ **Adverse Event** and/or ☐ **Product Problem** *(e.g., defects/malfunctions)*

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
   - ☐ Death: ____ *(mm/dd/yyyy)*
   - ☐ Life-threatening
   - ☐ Hospitalization - initial or prolonged
   - ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
   - ☐ Disability or Permanent Damage
   - ☐ Congenital Anomaly/Birth Defect
   - ☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of This Report *(mm/dd/yyyy)*

5. **Describe Event or Problem**

6. **Relevant Tests/Laboratory Data, Including Dates**

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

C. SUSPECT PRODUCT(S)

1. **Name** *(Give labeled strength & mfr/labeler)*
   #1
   #2

2. Dose, Frequency & Route Used	3. Therapy Dates *(If unknown, give duration) from/to (or best estimate)*
#1	#1
#2	#2

4. **Diagnosis for Use** *(Indication)*
   #1
   #2

5. **Event Abated After Use Stopped or Dose Reduced?**
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Exp. Date
#1	#1
#2	#2

8. **Event Reappeared After Reintroduction?**
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC# or Unique ID**

10. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name**

3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?** ☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

10. **Device Available for Evaluation?** *(Do not send to FDA)*
    ☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

11. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)*

E. INITIAL REPORTER

1. Name and Address	Phone #

2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA
☐ Yes ☐ No		☐ Yes ☐ No ☐ Unk.

MEDWATCH

FORM FDA 3500A (1/09) *(continued)*

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. **Check One** ☐ User Facility ☐ Importer
2. **UF/Importer Report Number**
3. **User Facility or Importer Name/Address**
4. **Contact Person**
5. **Phone Number**
6. **Date User Facility or Importer Became Aware of Event** *(mm/dd/yyyy)*
7. **Type of Report** ☐ Initial ☐ Follow-up # ____
8. **Date of This Report** *(mm/dd/yyyy)*
9. **Approximate Age of Device**
10. **Event Problem Codes** *(Refer to coding manual)*
    Patient Code ____ - ____ - ____
    Device Code ____ - ____ - ____
11. **Report Sent to FDA?** ☐ Yes ____ *(mm/dd/yyyy)* ☐ No
12. **Location Where Event Occurred** ☐ Hospital ☐ Home ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Outpatient Diagnostic Facility ☐ Ambulatory Surgical Facility ☐ Other: ____ *(Specify)*
13. **Report Sent to Manufacturer?** ☐ Yes ____ *(mm/dd/yyyy)* ☐ No
14. **Manufacturer Name/Address**

G. ALL MANUFACTURERS

1. **Contact Office - Name/Address** ***(and Manufacturing Site for Devices)***
2. **Phone Number**
3. **Report Source** *(Check all that apply)* ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other: ____
4. **Date Received by Manufacturer** *(mm/dd/yyyy)*
5. (A)NDA # ____ IND # ____ STN # ____ PMA/510(k) # ____ Combination Product ☐ Yes Pre-1938 ☐ Yes OTC Product ☐ Yes
6. **If IND, Give Protocol #**
7. **Type of Report** *(Check all that apply)* ☐ 5-day ☐ 7-day ☐ 10-day ☐ 15-day ☐ 30-day ☐ Periodic ☐ Initial ☐ Follow-up # ____
8. **Adverse Event Term(s)**
9. **Manufacturer Report Number**

H. DEVICE MANUFACTURERS ONLY

1. **Type of Reportable Event** ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Other: ____
2. **If Follow-up, What Type?** ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. **Device Evaluated by Manufacturer?** ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code: ____
4. **Device Manufacture Date** *(mm/yyyy)*
5. **Labeled for Single Use?** ☐ Yes ☐ No
6. **Evaluation Codes** *(Refer to coding manual)*
   Method ____ - ____ - ____ - ____
   Results ____ - ____ - ____ - ____
   Conclusions ____ - ____ - ____ - ____
7. **If Remedial Action Initiated, Check Type** ☐ Recall ☐ Repair ☐ Replace ☐ Relabeling ☐ Notification ☐ Inspection ☐ Patient Monitoring ☐ Modification/Adjustment ☐ Other: ____
8. **Usage of Device** ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. **If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:**
10. ☐ **Additional Manufacturer Narrative** and / or 11. ☐ **Corrected Data**

APPENDIX 5: NEW YORK HEART ASSOCIATION (NYHA) GUIDELINES

Class I	People whose physical activity is not limited. Ordinary physical activity does not cause undue fatigue, heart palpitations, trouble breathing, or chest pain.
Class II	People who have some limitation on physical activity. They are comfortable at rest, but ordinary physical activity causes fatigue, heart palpitations, trouble breathing, or chest pain.
Class III	People who have a marked limitation on physical activity. They are comfortable at rest, but less-than-ordinary physical activity causes fatigue, heart palpitations, trouble breathing, or chest pain.
Class IV	People who are unable to carry on any physical activity without discomfort. Symptoms may be present even at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX 6

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.

Genentech
BIOONCOLOGY

Appendix 7

SAFETY REPORTING FAX COVER SHEET

Investigator Sponsored Trials

SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Study Number (Genentech study number)	**AVF4762**
Principal Investigator	**Michael Overman, MD**
Site Name	**M. D. Anderson Cancer Center**
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date (DD/MON/YYYY)	____ / _____ /_____
Follow-up Report Date (DD/MON/YYYY)	____ / _____ /_____

Subject Initials (Please enter a dash if the patient has no middle name)	____ - ____ -____

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Please contact Genentech Safety for any questions regarding SAE or Safety reporting at (888) 835-2555