A Phase II Study of Capecitabine, Temozolomide and Bevacizumab for Metastatic or Unresectable Pancreatic Neuroendocrine Tumors

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Protocol Synopsis

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Study Centers: Stanford University School of Medicine (coordinating institution), , H. Lee Moffitt Cancer Center (subsite)

Number of subjects planned: 30 (20 at Stanford and 10 at Moffitt)

Planned accrual:

- 2-4 patients per month per site with enrollment complete in 18 months.
- Time on study per patient estimated at 6-9 months.
- Median follow-up at time of study completion estimated at 12 months.

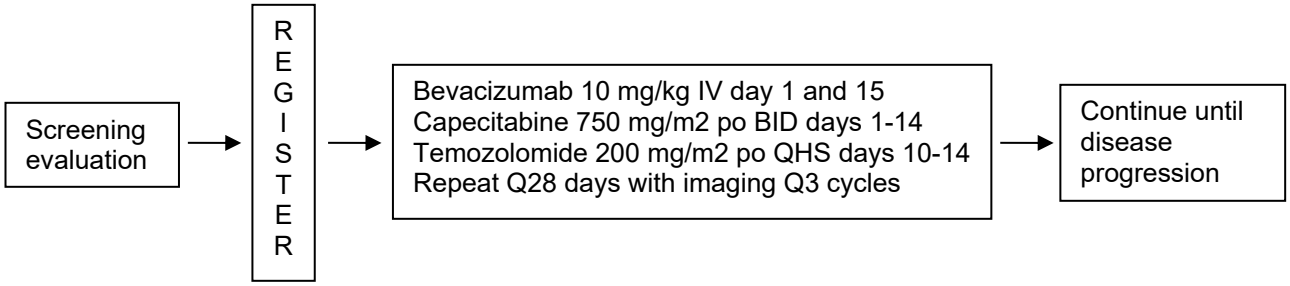
Objectives

1. Primary Objective
    a. To estimate the Radiographic Response Rate (RR), as defined by revised RECIST 1.1, under the combination of capecitabine and temozolomide with bevacizumab in patients with metastatic or unresectable pancreatic neuroendocrine tumors in comparison with the historical control rate.
    b. To assess the toxicities using CTCAE v4.0.

2. Secondary Objectives
    a. To evaluate progression-free survival (PFS) and overall survival (OS) using Kaplan-Meier analysis
    b. To assess MGMT by central path review
    c. To assess serum hormone marker levels
    d. To evaluate CT Perfusion as a tool to predict early therapeutic response (OPTIONAL)
    e. To bank serum for future correlative analyses

Study Design

We propose a multi-institution, phase II, single-arm, non-randomized study investigating bevacizumab in combination with capecitabine and temozolomide for unresectable or metastatic pancreatic neuroendocrine tumors. Treatment will be given every 28 days as per the schema outlined below. Patients will receive CT scans at baseline and after every 3 cycles (approximately 3 months) and be evaluated by RECIST criteria. We estimate that most patients will complete 6-9 cycles of treatment. Dose reductions are allowed after cycle 1. If, after 3 cycles, patients develop significant toxicities attributed to either temozolomide (including nausea, cytopenias, etc) or capecitabine (including diarrhea, hand-foot skin syndrome, etc) patients may discontinue these agents and continue receiving bevacizumab as a single agent. We will continue treatment indefinitely until one of the following occurs: patient withdraws consent and decides to discontinue study treatment, development of unacceptable toxicities, or evidence for progression of disease. If a patient is on single-agent bevacizumab at the time of disease progression, temozolomide and capecitabine may be restarted at the discretion of the investigator.



Target Subject Population

Patients with unresectable or metastatic pancreatic neuroendocrine tumors will be eligible for enrollment in this study. Patients must have measurable disease at the time of enrollment. No prior bevacizumab, fluoropyrimidine (capecitabine or 5FU) or temozolomide will be allowed. Prior sunitinib and everolimus will be allowed. Tumor tissue for MGMT analysis will be requested for centralized path review at Stanford (archival tissue is acceptable).

Investigational Products, Dosage and Mode of Administration

Bevacizumab**:**	10 mg/kg IV days 1 and 15 (28-day cycle)
Capecitabine:	750 mg/m2 PO BID days 1-14
Temozolomide:	200 mg/m2 PO QHS days 10-14

Comparator, Dosage and Mode of Administration

None.

Duration of Treatment

Each cycle lasts 28 days. Patients will continue on treatment until one of the following occurs:

1. Patient chooses to withdraw from study
2. Unacceptable toxicity occurs
3. Evidence of progressive disease by RECIST criteria
4. At the discretion of the investigator

Safety

Safety assessments will consist of routine and frequent monitoring and recording of all adverse events and serious adverse events, regular monitoring of hematology and serum chemistry, coagulation tests, urinalysis, regular measurement of vital signs, weight, WHO Performance Status and the performance of physical examination. The toxicities experienced by each patient on the study, and the study's overall progress, will be reviewed weekly at the Stanford University GI Oncology Research Meeting. Dose adjustments will be made at the discretion of the investigators as per protocol.

Statistical Methods

A sample size of 30 patients would give 80% power to reject the null RR of 40% if the true response rate (RR) is 65% or higher. The null hypothesis is based on a prospective phase II study conducted by Kulke, et al evaluating the efficacy of temozolomide and thalidomide[1]. In this study, 29 patients with mixed metastatic NETs were treated with temozolomide 150 mg/m^2 for 7 days every other week and thalidomide at doses of 50-400 mg daily. The overall radiographic response was 25% (45% in patients with pancreatic NETs). The alternative hypothesis is based on the more recent retrospective study in patients with pancreatic NETs reported by Strosberg, et al in which 30 patients were treated with capecitabine (750mg/m^2 twice daily, days 1-14) and temozolomide (200 mg/m^2 once daily, days 10-14) every 28 days; the RR was 70%.[2] RR is defined as the proportion of patients with complete response + partial response (CR+PR) based on a patient's best response. Progression-free survival (PFS) and overall survival (OS) will be evaluated using Kaplan-Meier analysis. For PFS analyses, patients will be censored at time last known alive if no progression has occurred.

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Appendix A: NCI Common Toxicity Criteria, v4.0 (website provided)
Appendix B: FDA MedWatch 3500a Form (website provided)
Appendix C: NYHA Guidelines (included)
Appendix D: Genentech Safety Reporting Cover Sheet (included)

ATTACHMENTS:
Attachment 1: Informed Consent Form (separate attachment)

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
ALT/SGPT	Alanine transaminase/Serum glutamate pyruvate transaminase
ANC	Absolute neutrophil count
AST/SGOT	Aspartate transaminase/Serum glutamic oxaloacetic transaminase
BID	Twice daily
BSA	Body surface area
CBC	Complete Blood Count
CI	Confidence interval
C_{max}	Maximum concentration of drug
CNS	Central Nervous System
CRC	Colorectal cancer
CRF	Case Report/Record Form
CR	Complete response
CrCl	Creatinine Clearance
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
5-FU	5-Fluorouracil
G-CSF	Granulocyte colony-stimulating factor (filgrastim)
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertension
IRB	Institutional Review Board
IV	Intravenous(ly)
LLN	Lower limit of normal
MGMT	O^6-alkyl guanine-DNA alkyltransferase
NSCLC	Non-small cell lung cancer
OS	Overall survival
PLT	Platelet
PO	Per os/by mouth/orally

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

1.0 Background

1.1 Disease Background

Neuroendocrine tumors (NETs) are a diverse group of malignancies that range from the well-differentiated carcinoid tumor to the poorly or undifferentiated neuroendocrine carcinoma. While localized disease may potentially be cured with surgical resection, systemic therapies for metastatic or unresectable disease have largely been ineffective.

Until recently there has been a paucity of randomized clinical trials using systemic therapies in this disease. However, two recent practice-changing studies have validated the use of new medications for this disease. The RADIANT-3 study[3], published in 2011, is a randomized Phase III study evaluating the efficacy of everolimus in advanced pancreatic NETs. A second randomized study evaluated the efficacy of sunitinib in advanced pancreatic NETs[4]. Both studies showed improvements in PFS favoring the treatment arms but did not show significant RRs. Yet, there is still a subset of patients in need of more dramatic response rates rather than just prolonged PFS. Recent reports of temozolomide and capecitabine in this disease have been encouraging. Temozolomide is an alkylating agent and shares an active metabolite with dacarbazine. In contrast to dacarbazine, temozolomide can penetrate the blood-brain barrier, is given orally, and has a more favorable side effect profile. Temozolomide has demonstrated modest single-agent efficacy for advanced NETs[5] but even more encouraging results when combined with capecitabine with reported response rates of 70% for pancreatic NETs[6]. MGMT deficiency is thought to be predictive of response to temozolomide and is more often associated with pancreatic NETs[7].

Additionally, NETs are highly vascular and have been shown to express high levels of vascular endothelial growth factor (VEGF). One of the first studies to incorporate an antiangiogenic strategy in this disease was a Phase II study using temozolomide and thalidomide in metastatic NETs that reported radiographic response rates of 25% (45% among pancreatic NETs, 33% among pheochromocytomas and 7% among carcinoid tumors.[1] A Phase II study using temozolomide and bevacizumab for metastatic carcinoid and pancreatic NETs also showed activity, with partial responses in 14% of all patients and stable disease in 79%[8]. Other data suggest that single-agent administration of bevacizumab for advanced carcinoid tumors results in inhibition of tumor blood flow and increases progression-free survival[9].

These prior studies have demonstrated encouraging results and acceptable toxicity profiles. We propose a multi-institution, phase II, single-arm, non-randomized study investigating bevacizumab in combination with temozolomide and capecitabine for patients with unresectable or metastatic neuroendocrine tumors.

1.2 Bevacizumab Clinical Experience

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. 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. 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).

1.2.1 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-CTC 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 or urinalysis at least every 4 weeks.

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-CTC 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; not 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 Thromboembolic 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.

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

Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

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).

Ovarian Failure: The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level≥30 mIU/mL and a negative serum β-HCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n=84 or with bevacizumab (n=95). New cases of ovarian failure were identified in 34% (32/95) of women receiving bevacizumab in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of bevacizumab treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the bevacizumab-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-

HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility. Long term effects of the treatment with bevacizumab on fertility are unknown. The risk of ovarian failure will be informed to female with reproductive potential and fertility preservation strategies will be discussed prior to starting treatment with bevacizumab.

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

1.3 Temozolomide Clinical Experience

Temozolomide is a second-generation oral alkylating agent that is currently approved for the treatment of patients with refractory anaplastic astrocytoma.[10,11] Several preclinical studies have demonstrated the activity of temozolomide against the leukemia cell lines.[12] Phase I studies in patients with relapsed/refractory acute leukemias suggested temozolomide was well tolerated and had significant antileukemic activity when administered as a single agent. The maximum tolerated dose for this group of patients was determined to be 200 mg/m^2/d for 7 days as induction and 200 mg/m^2/d for 5 days for postremission therapy.[13] A Phase II study confirmed the activity of temozolomide as a single agent in an elderly group of patients with poor risk disease AML.[14] Furthermore, this study demonstrated that AML patients can be further stratified into 2 very distinct groups of patients: Patients with no detectable expression of O^6-alkyl guanine-DNA alkyltransferase (MGMT) in leukemic blasts by Western blot had a complete response rate of 40% and overall response rate of 60%. In contrast, patients who had detectable MGMT in leukemic cells (85-90% of patients), had a 6% response rate to temozolomide (p=0.003 comparing absent vs. present MGMT expression).[14]

Temozolomide has demonstrated modest single-agent efficacy for advanced pancreatic NETs[5,15] but even more encouraging results in combination with other agents such as thalidomide[1] and fluoropyrimidines.[6,16,17] In particular, the Strosberg study showed particularly encouraging results[6]. In this retrospective study, 30 patients were treated with capecitabine (750mg/m2 twice daily, days 1-4) and temozolomide (200 mg/m2 once daily, days 10-14) every 28 days. Among 30 patients treated, 21 (70%) had objective radiographic responses. Median PFS was 18 months; OS at 2 years was 92%. A single arm Ph II prospective study of temozolomide and capecitabine for NETs is ongoing (R Fine (PI); NCT00869050).

1.3.1 Clinical Pharmacokinetics of Temozolomide

Absorption: Temozolomide is rapidly and completely absorbed after oral administration with a peak plasma concentration (Cmax) achieved in a median Tmax of 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and median Tmax increased by 2-fold (from 1–2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

A pharmacokinetic study comparing oral and intravenous temozolomide in 19 patients with primary CNS malignancies showed that 150 mg/m2 temozolomide for injection administered over 90 minutes is bioequivalent to 150 mg/m2 temozolomide oral capsules with respect to both Cmax and AUC of temozolomide and MTIC. Following a single 90-minute intravenous infusion of 150 mg/m2, the geometric mean Cmax values for temozolomide and MTIC were 7.3 mcg/mL and 276 ng/mL, respectively. Following a single oral dose of 150 mg/m2, the geometric mean Cmax values for temozolomide and MTIC were 7.5 mcg/mL and 282 ng/mL, respectively. Following a single 90-minute intravenous infusion of 150 mg/m2, the geometric mean AUC values for temozolomide and MTIC were 24.6 mcg·hr/mL and 891 ng·hr/mL, respectively. Following a single oral dose of 150 mg/m2, the geometric mean AUC values for temozolomide and MTIC were 23.4 mcg·hr/mL and 864 ng·hr/mL, respectively.

The pharmacokinetics of temozolomide were evaluated in selected patients with advanced cancer in phase I clinical trials. Single-dose pharmacokinetics were determined in nine patients after intravenous (IV) dosing ranging from 50 to 200 mg/m^2, and in 25 fasted patients following oral doses ranging from 200 to 1200 mg/m^2. Pharmacokinetic parameters obtained in these patients are summarized in the following table:

Parameter	Mean Value	N[a]	CV (%)[b]
Volume of distribution (L)	28.30	43	39
Elimination half life (hr)	1.81	48	20
Distribution half life (hr)	0.26	17	64
Clearance (L hr^{-1})	11.76	42	35

(a)N=number of observations (blood samples obtained).
(b)CV=coefficient of variation.

Oral bioavailability was studied by the CRC in five patients who received temozolomide both orally and intravenously as a one-hour infusion on two separate occasions at least four weeks apart. As shown in the following table, complete oral bioavailability was demonstrated in five of the subjects at 200 mg/m^2.

Patient Number	IV AUC[a] ($mg \cdot h \cdot L^{-1}$)	Oral AUC ($mg \cdot h \cdot L^{-1}$)	F[b]
5	32.16	41.00	1.27
7	33.12	32.32	0.98
15	35.96	41.67	1.16
17	23.55	31.94	1.36
19	25.30	16.93	0.67
			Mean: 1.09

(a)Area under the plasma concentration-time curve calculated by the trapezoidal rule.
(b)F= bioavailability calculated without consideration of the small differences in apparent elimination half life.

As part of SPRI phase I study 193-114-01, the pharmacokinetics of temozolomide were evaluated in 15 adult patients on days 1 and 5 of treatment (3 patients each at oral doses of 100, 150, or 250 mg/m^2/day, and 6 patients at 200 mg/m^2/day). Temozolomide was rapidly absorbed (mean T_{MAX} range=0.33-1.50 hr) and rapidly eliminated (mean total body clearance, CL/F=~200 m./min) following 5 consecutive days of administration. Elimination half-life was 1.8 hr. Pharmacokinetic parameters were similar on days 1 and 5, and temozolomide did not accumulate in plasma upon multiple dosing. Systemic exposure (AUC) increased linearly as dose increased from 100 to 250 mg/m^2/day. Intra- and inter-subject variability in plasma concentrations and pharmacokinetic parameters were small.

Distribution: Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively.

Excretion: About 38% of the administered temozolomide total radioactive dose is recovered over 7 days: 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m2. Temozolomide is rapidly eliminated, with a mean elimination half-life of 1.8 hours, and exhibits linear kinetics over the therapeutic dosing range of 75 to 250 mg/m2/day.

Effect of Age: A population pharmacokinetic analysis indicated that age (range: 19–78 years) has no influence on the pharmacokinetics of temozolomide.

Effect of Gender: A population pharmacokinetic analysis indicated that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men.

Effect of Race: The effect of race on the pharmacokinetics of temozolomide has not been studied.

Effect of Tobacco Use: A population pharmacokinetic analysis indicated that the oral clearance of temozolomide is similar in smokers and nonsmokers.

Effect of Renal Impairment: A population pharmacokinetic analysis indicated that creatinine clearance over the range of 36 to 130 mL/min/m2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr <36 mL/min/m2). Caution should be exercised when temozolomide is administered to patients with severe renal impairment.

Effect of Hepatic Impairment: A study showed that the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child-Pugh Class I – II) were similar to those observed in patients with normal hepatic function.

Effect of Other Drugs on Temozolomide Pharmacokinetics: In a multiple-dose study, administration of temozolomide capsules with ranitidine did not change the Cmax or AUC values for temozolomide or MTIC.

A population analysis indicated that administration of valproic acid decreases the clearance of temozolomide by about 5%.

A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

1.3.2 Adverse Reactions:

The most common reactions to Temozolomide include nausea, vomiting, headache, fatigue and hematologic effects. These events are usually mild to moderate. Nausea and vomiting is usually readily controlled with antiemetics. Myelosuppression (thrombocytopenia and neutropenia) is the dose-limiting side effect. It usually occurs within the first few cycles of therapy and is not cumulative. In prior studies, myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. Cases of hepatic injury, including fatal hepatic failure, have been reported infrequently in patients receiving temozolomide. Liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. For patients with significant liver function abnormalities the benefits and risks of continuing treatment will be carefully considered.

Other less common side effects may include somnolence or insomnia, anorexia, constipation, diarrhea, weight loss, abdominal pain, rash, pruritis, anxiety, depression, pain when swallowing, hyperglycemia,] =-kidney abnormalities, Stevens-Johnson-Syndrome, PCP infection, secondary malignancy, and aplastic anemia.

1.3.3 MGMT Methylation Status

The MGMT gene is located on chromosome 10q26 and encodes a DNA-repair protein that removes alkyl groups from the O^6 position of guanine, an important site of DNA alkylation. The restoration of the DNA consumes the MGMT protein, which the cell must replenish. Left unrepaired, chemotherapy-induced lesions, especially O^6-methylguanine, trigger cytotoxicity and apoptosis.[18] Epigenetic silencing of the MGMT gene by promoter methylation is associated with loss of MGMT protein expression[19,20] and diminished DNA-repair activity. Based on these findings, several studies have shown that MGMT epigenetic silencing through promoter methylation, as determined by methylation-specific polymerase-chain-reaction analysis, was an independent favorable prognostic factor in patients with glioblastoma multiforme treated with temozolomide.[18,21]

Interestingly, there is compelling evidence that protracted schedules of temozolomide may lead to an 'autoenhancement' of its inherent cytotoxic potential by cumulative reduction of the cell's capacity for MGMT-mediated DNA repair and resistance. O^6-alkyl guanine-DNA alkyltransferase activity was measured in the PBMCs of patients treated on two phase I protracted temozolomide studies. Patients were treated daily with various temozolomide doses (75-175 mg m^{-2}) and treatment duration (7-21 days), and levels of MGMT inactivation and regeneration, as well as the relation between MGMT inactivation and toxicity, were studied. This study determined that protracted, relatively low-doses (100mg/m^2) of temozolomide given daily for 14 days leads to marked inactivation of MGMT (~80%).[22]

1.4 Capecitabine Clinical Experience

Capecitabine is an oral fluoropyrimidine that mimics continuous infusion 5-FU and has since replaced it in the treatment of many gastrointestinal malignancies. The conversion to 5-FU is dependent on the enzyme thymidine phosphorylase, which is more highly expressed in tumor tissue than healthy tissue resulting in the preferential generation of 5-FU at the tumor site[23]. Capecitabine is currently approved in the United States for treatment of advanced breast and colorectal cancers.

1.4.1 Capecitabine Safety Profile

Capecitabine Monotherapy –in Colorectal and Breast carcinoma: The safety database for monotherapy consists of 630 patients with mCRC from two phase III studies and one phase II study and 319 patients with metastatic breast cancer from four phase II studies. The most frequently reported adverse events (AEs) among patients receiving capecitabine monotherapy as treatment for breast and CRC were hand-foot syndrome (HFS), diarrhea, nausea, vomiting, stomatitis and fatigue. The majority of treatment-related AEs were mild to moderate in intensity. The treatment-related grade 3and 4 AEs with the highest incidences were HFS (grade 3 only), diarrhea, and nausea.

Most of the grade 4 treatment-related AEs was in the gastrointestinal (GI) system. The incidence of treatment-related serious AEs (SAEs) was low. The most frequent treatment-related SAEs (i.e., those reported in ≥2% of patients) were diarrhea, dehydration, vomiting, nausea, and stomatitis. HFS was reported as a SAE in only two patients (<1%). The overall safety profile of capecitabine monotherapy as adjuvant treatment for stage III colon cancer was similar to that observed in the pooled monotherapy metastatic CRC and breast cancer safety database.

Capecitabine in combination with oxaliplatin and bevacizumab (XELOX+BV) in colorectal cancer: the most frequently occurring AEs in patients with mCRC who received first-line treatment with XELOX+BV were nausea, vomiting and parasthesia. There was a moderate increase in the incidence of vomiting and PPE. Diarrhea was the most common grade 3/4 AE (unrelated and related to treatment) as well as the most common treatment-related SAE. An increase in the incidence of vascular disorders was observed, mainly due to the incidence of deep vein thrombosis.

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

1.5 Study Rationale

Recent temozolomide-based studies in pancreatic NETs have demonstrated encouraging results and acceptable toxicity profiles. Temozolomide can safely be combined with capecitabine and may in fact be synergistic.[2] Additionally, temozolomide can safely be combined with bevacizumab[8]. For patients who need an objective response (due to rapid disease progression, bulky tumors, or symptomatic disease) we are in need of a well-tolerated regimen that yields high response rates. To date, the temozolomide/capecitabine restrospective data is the most promising chemotherapy backbone. There is sound scientific rationale that bevacizumab is also active in this disease and will hopefully be additive or synergistic with temozolomide/capecitabine. Capecitabine and Bevacizumab are routinely used safely in the setting of metastatic colorectal cancer. We do not anticipate safety issues for the Temozolomide/Capecitabine/Bevacizumab drug combination. We, therefore, propose a multi-institution, phase II, single-arm, non-randomized study investigating bevacizumab in combination with temozolomide and capecitabine for patients with unresectable or metastatic pancreatic neuroendocrine tumors.

1.6 Correlative Studies Background

CT perfusion will be performed on all patients who consent to the imaging research study.

Tissue will be obtained from all patients who consent to participate in banking.

Blood will be obtained from all patients who consent to participate in the laboratory research studies.

CT Perfusion:

Perfusion computed tomography (CT) imaging has been established for many years in stroke imaging. With the introduction of multi-detector row CT technology increasing substantially the spatial and temporal resolution as well as offering new detector array configurations, CT perfusion imaging has become feasible for assessment of tumor perfusion in applications outside the brain, including the abdomen. Recent studies indicate that perfusion CT can be performed successfully in patients with NETs.[24,25] Different parameters of tumor perfusion have been assessed in patients with NETs and compared to normal tissue including blood flow (BF), blood volume (BV), mean transit time (MTT), time to peak (TTP), permeability surface, and volume transfer constant (K^{trans}). The implications of those parameters on grade of tumor vascularization, correlation with ex vivo parameters of angiogenesis including microvessel density (MVD), or expression profiles of molecular markers of tumor angiogenesis such as vascular endothelial growth factor receptor (VEGFR) or integrins in NETs still need to be assessed. However, a recent study in patients with pancreatic endocrine tumors undergoing preoperative perfusion CT has shown high correlation between the tumor BV parameter as assessed by perfusion CT and ex vivo MVD analysis, as well as histoprognostic factors such as proliferation index and WHO classification obtained from tumor samples.[26] Another recent study in patients with locally advanced pancreatic cancer has shown that the parameter K^{trans} may be a valuable quantitative biomarker for predicting favorable treatment response to concurrent chemotherapy and radiotherapy.[27]

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

In this phase II protocol using bevacizumab with capecitabine and temozolomide for metastatic or unresectable pancreatic NETs we propose to include CT perfusion imaging as an integral part of the regular CT imaging protocol. Isovue 370 will be used as the intravenous contrast agent. The premixed agent from Bracco will be used up to 120 ml depending on patient weight for diagnostic CT, 50 ml for perfusion CT portion The perfusion portion of the CT Scan will take a few extra minutes and the dose will be approximately 24-28 mSv of radiation which is just over half the dose of a normal CT study. The CT perfusion part can be included into the standard baseline and 3-month follow-up CT scan. In addition, we propose to include an early, 2-week dedicated CT perfusion examination to assess functional perfusion data shortly after the first doses of bevacizumab.

MGMT testing:

Evaluation of MGMT status by Immunohistochemistry (IHC)

Temozolomide is an alkylating agent initially developed as an oral and more easily tolerated alternative to dacarbazine. The cytotoxic effect of temozolomide has been

attributed to its ability to induce DNA methylation at the O6 position of guanine. Methylation of guanine results in DNA mismatch, ultimately resulting in apoptosis and tumor cell death.[17] The sensitivity of tumor cells to alkylating agents, including temozolomide, has been associated with decreased levels of the DNA repair enzyme, O6-methylguanine DNA methyltransferase (MGMT), which, through its ability to restore DNA to its normal form, can prevent chemotherapy-induced cell death.[18] Decreased levels of MGMT have been associated with clinical benefit and enhanced survival in melanoma and glioblastoma patients treated with temozolomide.[19-23]
In a study by Kulke, et al., 97 archival neuroendocrine tumors specimens were evaluated for MGMT deficiency by immunohistochemistry.[8] Among 37 pancreatic neuroendocrine tumors evaluated, 19 (51%) were MGMT deficient. Non-functional tumors included similar proportions of MGMT intact and MGMT deficient tumors. Three of 10 insulinomas were MGMT deficient; both gastrinomas and the single evaluated glucagonoma were also MGMT deficient. In contrast, MGMT was present in all 60 carcinoid tumors (20 typical bronchial carcinoids, 20 atypical bronchial carcinoids and 20 small intestine carcinoids) evaluated. Among 21 patients with evaluable tumor tissue who had also received treatment with temozolomide, 4 of 5 patients with MGMT-deficient tumors (all pancreatic NETs) and 0 of 16 patients with MGMT-intact tumors responded to treatment (p=0.001).

Evaluation of MGMT status by Promoter Methylation
The clinical utility of assessing MGMT promoter methylation status was first demonstrated in patients with gliomas. Gliomas are the most common primary brain tumors. Grade IV gliomas, also known as glioblastoma multiforme (GBM) are highly malignant tumors that account for almost a third of primary brain tumors in adults. Patients with gliomas that exhibited promoter methylation of the MGMT gene showed modestly longer survival after treatment with alkylating chemotherapeutics than patients whose gliomas did not show MGMT promoter methylation. Clinical trials to evaluate the use of MGMT promoter methylation to predict response to alkylating agents have also been designed for patients with acute myeloid leukemia, neuroendocrine tumors, and other cancers.

The mechanisms of MGMT regulation in neuroendocrine tumors remain unknown. Silencing of the MGMT gene by CpG island promoter methylation is a common mechanism of MGMT regulation in other tumor types. In patients with glioblastoma, MGMT promoter methylation is associated with improved survival and benefit from temozolomide.[22,24] Limited studies of CpG island methylation in neuroendocrine tumors however, have found either no significant difference in MGMT promoter methylation rates between carcinoid and pancreatic neuroendocrine tumors, or higher rates of promoter methylation in carcinoid tumors compared to pancreatic neuroendocrine tumors.[25,26]

Further studies to evaluate whether promoter methylation is a common MGMT silencing mechanism in neuroendocrine tumors, and whether promoter methylation correlates with immunohistochemical absence of MGMT, are warranted.

2.0 Objectives

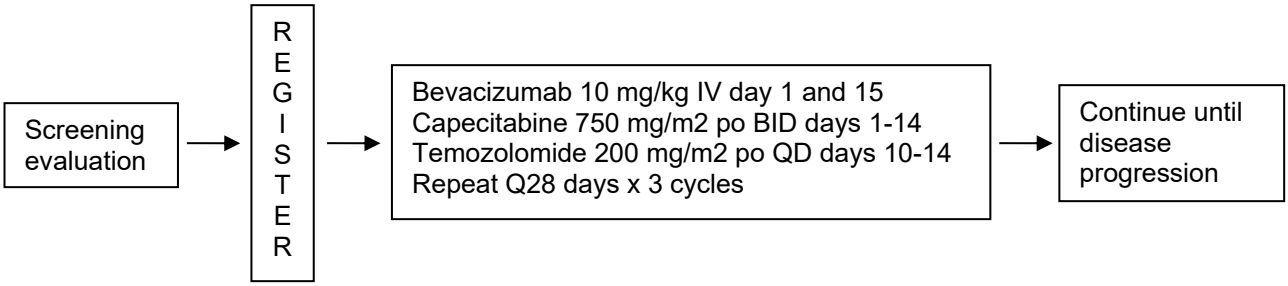
a. Primary Objective
   i. To investigate if the combination of capecitabine and temozolomide with bevacizumab for metastatic or unresectable neuroendocrine tumors will improve RR by 62% over historical controls (null RR of 40% to true RR 65%).
   ii. Assess the toxicities using CTCAE v4.0.

b. Secondary Objectives
   i. To evaluate progression-free survival (PFS) and overall survival (OS) using Kaplan-Meier analysis
   ii. To assess MGMT by central path review
   iii. To assess serum hormone marker levels
   iv. To evaluate CT Perfusion as a tool to predict early therapeutic response (OPTIONAL)
   v. To bank serum for future correlative analyses

3.0 Study Design

3.1 Description of the Study

We propose a multi-institution, phase II, single-arm, non-randomized study investigating bevacizumab in combination with capecitabine and temozolomide for unresectable or metastatic pancreatic neuroendocrine tumors. Treatment will be given every 28 days as per the schema outlined below. Patients will receive CT scans at baseline and after every 3 cycles (approximately 3 months) and be evaluated by RECIST criteria. We estimate that most patients will complete 6-9 cycles of treatment. Dose reductions are allowed after cycle 1. If, after 3 cycles, patients develop significant toxicities attributed to either temozolomide (including nausea, cytopenias, etc) or capecitabine (including diarrhea, hand-foot skin syndrome, etc) patients may discontinue these agents and continue receiving bevacizumab as a single agent. We will continue treatment indefinitely until one of the following occurs: patient withdraws consent and decides to discontinue study treatment, development of unacceptable toxicities, or evidence for progression of disease. If a patient is on single-agent bevacizumab at the time of disease progression, temozolomide and capecitabine may be restarted at the discretion of the investigator.



This will be a Phase II study evaluating capecitabine, temozolomide, and bevacizumab in patients with unresectable or metastatic pancreatic neuroendocrine tumors.

A sample size of 30 patients would give 80% power to reject the null RR of 40% if the true RR is 65% or higher. The null hypothesis is based on a prospective phase II study conducted by Kulke, et al evaluating the efficacy of temozolomide and thalidomide.[1] In this study, 29 patients with mixed metastatic NETs were treated with temozolomide 150 mg/m^2 for 7 days every other week and thalidomide at doses of 50-400 mg daily. The overall radiographic response was 25% (45% in patients with pancreatic NETs). The alternative hypothesis is based on the more recent retrospective study reported by Strosberg, et al in which patients were treated with capecitabine (750mg/m^2 twice daily, days 1-14) and temozolomide (200 mg/m2 once daily, days 10-14) every 28 days[6]. Of 30 patients treated, the RR was 70%.

3.2 Rationale for Study Design

We selected a single arm study as the best way to determine preliminary efficacy and safety of this regimen for pancreatic NETs. We have chosen a multisite study for this rare disease to enhance accrual rates. Our planned doses of bevacizumab, capecitabine, and temozolomide are routinely used in GI and other malignancies.

3.3 Outcome Measures

3.3.1 Primary

a. RR % (by RECIST v1.1)
b. Toxicities according to CTCAE v4.0.

3.3.2 Secondary

c. PFS (median in months) and OS (median in months)
d. MGMT by central pathology review
e. Serum hormone marker analysis
f. CT perfusion
    i. Correlation of the CT perfusion parameters with:
        1. Progression free survival
        2. Overall survival
        3. RECIST criteria
    ii. Correlation of early perfusion parameters (from baseline, 2-week, and 9-week follow-up scans)
g. Serum to be stored for future correlative studies

3.3.3 Safety Outcome Measures

Toxicities will be assessed per CTCAE v4.0. Patients will be monitored for systemic, renal, gastrointestinal, hematologic, neurological and liver toxicities. Specifically, patients will have laboratory tests (including CBC with differential and comprehensive metabolic panel) performed every 4 weeks. In addition, patients will be seen in the clinic for history and physical and assessed for side effects and toxicities every 4 weeks.

4.0 Safety Plan

4.1 Bevacizumab-specific

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria 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 (28–42 days) after the decision to discontinue treatment.

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 dipstick, urinalysis, or 24hour urine and graded as shown in the following table.[31,32] Proteinuria will be managed per guidelines outlined in section 6.1.3

Protein dipstick grading		
Designation	**Approx. amount**	
	Concentration	Daily
Trace	5–20 mg/dL	
1+	30 mg/dL	Less than 0.5 g/day
2+	100 mg/dL	0.5–1 g/day
3+	300 mg/dL	1–2 g/day
4+	More than 300 mg/dL	More than 2 g/day

- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure.

Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk after surgery). Temozolomide and/or capecitabine may also be held at the discretion of the investigator.

4.2 Other Study Drug(s)-Specific

Please see Section 6.0 for detailed instructions for the management of study drug–related toxicities.

5.0 Study Subjects

5.1 Inclusion Criteria

1. Patients must have histologically confirmed pancreatic neuroendocrine tumors that are considered low or intermediated grade as defined by Klimstra, et al (to include Ki-67 and mitotic index).[28]
2. Patients must have metastatic or unresectable disease
3. Patients with prior surgical resection who develop radiological or clinical evidence of metastatic cancer do not require separate histological or cytological confirmation of metastatic disease unless an interval of > 5 years has elapsed between the primary surgery and the development of metastatic disease. Clinicians should consider biopsy of lesions to establish diagnosis of metastatic disease if there is substantial clinical ambiguity regarding the nature or source of apparent metastases.
4. Prior sunitinib and everolimus will be permitted. A wash-out period of 2 weeks is required prior to first dose on this study.
5. Concurrent somatostatin analogues are allowed provided that patients 1) have been on stable doses x 8 weeks and 2) have documented disease progression on that dose.
6. Prior liver directed therapies will be permitted (ie. chemoembolization, radioembolization) as long as target lesions in the liver have demonstrated growth since the liver directed treatment.
7. Prior peptide receptor radionuclide therapy (PRRT) will be permitted as long as target lesions in the liver have demonstrated growth since the liver directed treatment.
8. Low-dose aspirin (≤ 325 mg/d) may be continued in subjects at higher risk for arterial thromboembolic disease.
9. Patients must have a primary or metastatic lesion measurable in at least one dimension by Modified RECIST criteria v1.1 (see Section 4.2) within 4 weeks prior to entry of study.

10. Patients must have ECOG performance status of 0-2
11. Patients must be ≥ 18 years of age.
12. Laboratory values ≤ 2 weeks prior to start date (may be supported by transfusion and/or hematopoetic growth factors):
    - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L (≥ 1500/mm^3)
    - Platelets (PLT) ≥ 100 x 10^9/L (≥ 100,000/mm^3)
    - Hemoglobin (Hgb) ≥ 9 g/dL
    - Serum creatinine ≤ 1.5 x ULN
    - Serum bilirubin ≤ 1.5 x ULN
    - Aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT) ≤ 3.0 x ULN (≤ 5.0 x ULN if liver metastases present). Note: ERCP or percutaneous stenting may be used to normalize the liver function tests.
13. Life expectancy ≥ 12 weeks.
14. Ability to give written informed consent according to local guidelines.

5.2 Exclusion Criteria

Disease-Specific Exclusions

1. Prior bevacizumab and any cytotoxic chemotherapy.
2. Poorly differentiated or high grade pancreatic neuroendocrine tumors
3. Prior full field radiotherapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior to enrollment. Patients must have recovered from all therapy-related toxicities. The site of previous radiotherapy should have evidence of progressive disease if this is the only site of disease.
4. Diagnosis of another malignancy, unless the patient was diagnosed at least 3 years earlier and has been disease-free for at least 6 months following the completion of curative intent therapy, specifics as follows:
    - Curatively resected non-melanomatous skin cancer
    - Curatively treated cervical carcinoma in situ
    - Patients with organ-confined prostate cancer with no evidence of recurrent or progressive disease based on prostate-specific antigen (PSA) values are also eligible for this study if hormonal therapy has been initiated or a radical prostatectomy has been performed.

- Other primary solid tumor curatively treated with no known active disease present and no treatment administered for the last 3 years.

5. Concurrent use of other investigational agents and patients who have received investigational drugs ≤ 4 weeks prior to enrollment.
6. Known hypersensitivity to capecitabine, temozolomide, or any component of the formulation and or a known deficiency of dihyropyrimidine dehydrogenase.

General Medical Exclusions

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

7. Inability to comply with study and/or follow-up procedures.
8. Current, recent (within 4 weeks of the first infusion of this study), or planned participation in an experimental drug study.
9. Pregnancy (positive pregnancy test) or lactation- breast feeding Lack of of effective means of contraception (men and women) in subjects of child-bearing potential.
10. Uncontrolled systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
11. Known history of HIV, HBV, or HCV
12. Current, ongoing treatment with full-dose warfarin. However patients may be on stable doses of a low molecular weight heparin are allowed (ie. Lovenox).

Bevacizumab-Specific Exclusions

13. Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg).
14. Prior history of hypertensive crisis or hypertensive encephalopathy.
15. New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix E).
16. History of myocardial infarction or unstable angina within 6 months prior to Day 1.
17. History of stroke or transient ischemic attack within 6 months prior to Day 1.
18. Known CNS metastases
19. Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1.

20. History of GI bleeding (hemoptysis/melena/hematochezia, $\geq$ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1.
21. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
22. 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.
23. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1.
24. History of abdominal fistula or gastrointestinal perforation within 6 months prior to Day 1.
25. Serious, non-healing wound, active ulcer, or untreated bone fracture.
26. Proteinuria: Patients are allowed to have 0, trace, or 1+ protein by urine dipstick or urinalysis to enroll, if >= 2+ must check 24h urine protein and must be < 1g to start study.
27. Known hypersensitivity to any component of bevacizumab.

6.0 Study Medications

6.1 Bevacizumab administration, storage, and toxicity management

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

Bevacizumab will be supplied by Genentech/Roche as the commercially available form of this medication.

For further details and molecule characterization, see the bevacizumab Investigator Brochure.

6.1.1 Bevacizumab Administration

Bevacizumab will be initiated at a dose of 10 mg/kg IV on days 1 and 15 of a 28-day cycle. Dose will be based on actual weight and subsequent doses will remain the same unless there is a +/- 5% change from the actual weight.

It 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.

6.1.2 Bevacizumab Storage

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

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

6.1.3 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 v4.0 Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's symptoms

have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

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

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

Table1:
Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hypertension	
No dose modifications for grade 1/2 events	
Grade 3	If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including 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	
Grade 3 or 4	Hold bevacizumab. 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 (note: urine protein-to-creatinine ratio <u>not</u> allowed**)**	
Grade 1	No bevacizumab dose modifications.
Grade 2	Suspend bevacizumab for ≥ 2 grams / 24 hours, and resume when proteinuria is < 2 grams / 24 hours. For 2+ urinalysis/dipstick: Ok to treat, but obtain 24 hour urine prior to next bevacizumab dose. For 3+ urinalysis/dipstick: Ok to treat, but obtain 24 hour urine prior to bevacizumab dose.
Grade 3	Suspend bevacizumab. Resume when proteinuria is < 2 grams / 24 hours as determined by 24 hour urine collection
Grade 4 (nephrotic 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.
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.
Hematological Toxicities (for Day 15, Bevacizumab infusion only)	
ANC	
Grade 1/2/3	No dose modifications
Grade 4	Hold dose
Platelets	
Grade 1/2	No dose modifications
Grade 3/4	Hold dose

6.2 Temozolomide administration, storage, and toxicity management

Temozolomide [8-carbamoyl-3-methylimidazo(5,1-d)-1,2,3,5-tetrazin-4(3H)-one] (Temodal) is an imidazole tetrazinone compound developed by Schering-Plough for use as an antineoplastic agent. TMZ is a prodrug that spontaneously hydrolyzes to 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC), which is also the active metabolite of dacarbazine. Dacarbazine, however, requires hepatic metabolism for formation of this metabolite, which results in variable levels. TMZ is stable at an acidic pH, allowing oral absorption, and has a broad biodistribution.

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions of guanine.

The inactive ingredients for temozolomide Capsules are as follows: lactose anhydrous (132.8 mg), colloidal silicon dioxide (0.2 mg), sodium starch glycolate (7.5 mg), tartaric acid (1.5 mg), and stearic acid (3 mg).

The body of the capsules are made of gelatin, and are opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, and ferric oxide.

Temozolomide capsules are supplied in amber glass bottles containing 5, 14, or 20 capsules per bottle. Temozolomide is supplied in preservative free, 2-piece hard gelatin capsules in the following p.o. dose strengths: 5mg. 20mg. 100mg. 140mg. 180mg, and 250mg. Each capsule contains the active drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lautyl sulfate NF. Temozolomide is commercially available. Temozolomide is supplied in preservative free, 2-piece hard gelatin capsules.

Agent Ordering

Temozolomide is being provided by Merck. Commercial Temozolomide will be used in this study. Temozolomide will be shipped directly to all sub-sites from Merck.

6.2.1 Temozolomide Administration:

Oral temozolomide will be given at a dose of 200 mg/m^2 PO once daily for days 10-14 at bedtime. Body Surface Area (BSA) will be calculated based on adjusted ideal body weight. The temozolomide dose will be capped at 400 mg daily and given as only 100 or 180 mg capsules. Ondansetron will be given as a premedication to prevent nausea 30-60 min prior to the temozolomide dose. Temozolomide should be taken by mouth after fasting from solid food for two hours. Temozolomide tablets must not be crushed and must be administered whole. Temozolomide missed doses will not be made up, and patients should not double-up on missed doses during treatment.

6.2.2 Temozolomide Storage:

As a solid, temozolomide is thermally stable and does not decompose when exposed to light. In solution, temozolomide undergoes rapid hydrolysis in a basic environment. The product label recommends storage at room temperature 25°C (77°F). Temozolomide should be stored at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F). Care will be taken to maintain an acceptable storage temperature. The clinical supplies storage area at the site will be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring will be maintained on site.

Agent Accountability

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the manufacturer, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. Stanford pharmacy must be kept informed of subsite drug shipments, use, and destruction.

In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (i.e., when counting returns). The Principal Investigator, Stanford study coordinator, or the investigative pharmacy at Stanford should be contacted with any questions concerning investigational products where special or protective handling is indicated.

Due to biohazard concerns, unused study drug will be destroyed locally and not sent back to Merck & Co, Inc. Drug will be destroyed according to standard operating procedures of the institutional pharmacy.

Drug accountability: temozolomide may not be used outside the scope of this protocol, nor can temozolomide be transferred or licensed to any party not participating in this clinical study. Opened bottles returned by patients should be documented in the patient-specific investigational Agent Accountability Record (i.e. logged in as “returned by patients” and logged out as “for destruction”) and destroyed on-site in accordance with institutional policy.

6.2.3 Temozolomide Dose Modifications:

The dose of temozolomide will be determined according to (1) non-hematologic AEs during the previous cycle, as well as (2) the lowest ANC and platelet counts during that cycle.

- Dose reductions: For non-hematologic grade 3 AEs (except for nausea and vomiting as well as AEs unrelated to treatment) the dose should be reduced according to the Temozolomide Dose Level Table. Dose reductions for treatment day ANC and platelet counts should also be made according to the Dose Level Table below. Each dose reduction will be a 20% reduction from the prior level. No dose escalation of temozolomide is permitted

- Discontinuation: For patients who require more than 2 dose reductions, temozolomide will be permanently discontinued. For any non-hematologic drug-related grade 4 AEs that does not resolve within the allowed 4 weeks, then temozolomide treatment will be permanently discontinued. Also, except for nausea and vomiting, if any of the same non-hematologic grade 3 AEs that are at least possibly related to study treatment recur after reduction for that AE, then temozolomide will be stopped.

Temozolomide Dose Level Table	
Dose Level	Dose in mg/m^2
0	200
-1	160
-2	128

* Note this is a 20% dose reduction with each dose level

Hematologic Toxicity

ANC (/mm^3)		**Platelets (/mm^3)**	**% of Planned Temozolomide**
> 1500/mm^3	And	> 100,000/mm^3	100%
750-1499/mm^3	Or	50,000-99,999/mm^3	Hold then dose reduce*
< 750/mm^3	or	< 50,000/mm^3	Hold then dose reduce**

*Upon recovery to ANC ≥ 1,500/mm^3 and platelets to ≥ 100,000/mm^3, the dose level -1 will be administered (160 mg/m2). Discontinue dose if patients do not recover within ≤ 4 weeks. If patient was already receiving Temozolomide at the -1 dose level, reduce to the -2 dose (128 mg/m2).

**Upon recovery to ANC ≥ 1,500/mm^3 and platelets to ≥ 100,000/mm^3, the dose level -2 will be administered (128 mg/m2). Discontinue dose if patients do not

recover within ≤ 3 weeks. If patient was already receiving Temozolomide at the -2 dose level, treatment should be discontinued.

Non-hematologic Toxicity

For non-hematologic toxicities, dose reductions of temozolomide will be at the discretion of the investigator. Dose-reductions should follow the Temozolomide Dose Level Table above. A maximum of 2 dose reductions can be performed.

6.3 Capecitabine administration, storage, and toxicity management

Capecitabine will be dosed at 750 mg/m^2 PO BID for days 1-14. The dose will be capped at 1500 mg PO BID. The dose will be rounded to the nearest 500 mg. Adjusted ideal body weight will be used for BSA calculations.

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

Capecitabine will be supplied by Genentech/Roche as the commercially available form of this medication.

For further details and molecule characterization, see the Capecitabine Investigator Brochure.

6.3.1 Capecitabine Administration

Capecitabine will be administered at an initial dose of 750 mg/m2 by mouth twice daily, on days 1-14 of a 28-day cycle.

Capecitabine is supplied as biconvex, oblong film-coated tablets, available as 150 mg tablets (light peach) and 500 mg tablets (peach). Capecitabine is stored at 25 °C, with excursions permitted to 15 to 30 °C.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. The calculated dose by body surface area (BSA) will be rounded down to allow doses using 500 mg tablets.

6.3.2 Capecitabine Dose Modification and Toxicity Management

Capecitabine will be initiated at 750 mg/m2 PO BID x 14 days on a 28-day cycle.

Two total dose reductions are permitted before capecitabine will be discontinued.

Hematologic Toxicities

ANC (/mm³)		Platelets (/mm³)	Modification
<1500/mm^3	AND/OR	< 100,000/mm^3	Hold until ANC ≥ 1500/mm^3 and PLT ≥ 100,000/mm^3; resume at 20% dose reduction
≥ 1500/mm^3	AND	≥ 100,000/mm^3	No dose modification

Mucositis, Diahhrea, or Esophagitis

Grade	Toxicities/Symptoms	Modification
1	Mucositis,diarrhea, or esophagitis	No dose modification
2	Diarrhea	No dose modification
2	Mucositis or esophagitis	Hold until ≤ grade 1; resume at 20% dose reduction
3	Diarrhea	Hold until ≤ grade 1 ;resume at 20% dose reduction
3/4	Mucositis or esophagitis	Hold until ≤ grade 1; resume at 20% dose reduction

Hand and Foot Rash

Grade	Modification
1	No dose modification
2	Hold until symptoms resolve to grade 0 or 1. Resume at 20% dose reduction.
≥ 3	Hold until symptoms resolve to grade 0 or 1. Resume at 20% dose reduction.

Non-hematologic Toxicity

For other non-hematologic toxicities, dose reductions of capecitabine will be at the discretion of the investigator. A 20% dose reduction should be performed with each subsequent reduction. A maximum of 2 dose reductions can be performed.

6.4 General Dose Modifications

All toxicity grades above are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Dose reduction will be based on day 1 labratory values of each cycle.

Dose reductions will be based on current dose. If dose reduction is required, reduction is permanent. Missed doses will not be made up.

Dose will be modified for all drugs if there is a ≥ 5% change in patient's weight while on study.

If multiple toxicities are seen, the dose administered in a subsequent cycle should be based on the most severe toxicity experienced in the current cycle.

AEs determined to be unrelated to study treatment will not require dose reduction.

If toxicities have not resolved within ≤ 4 weeks of next planned cycle start date, patients must discontinue protocol treatment.

After 3 cycles of treatment, any of the three drugs can be discontinued at the investigator's discretion for any adverse event with severity of grade 3 or more.

If patient is on maintenance bevacizumab, upon documentation of first disease progression by RECIST criteria, the patient can restart the original schedule of temozolomide, capecitabine, and bevacizumab at the investigator's discretion.

6.5 Concomitant and Supportive Medications

6.5.1 Concomitant medications

Capecitabine Drug Interactions

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

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

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

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

6.5.2 Pre-medications

Ondansetron is required as a premedication 30 minutes prior to temozolomide. Otherwise, anti-emetics, anxiolytics, and analgesics may be provided at physicians' discretion.

6.5.3 Supportive Care Guidelines

Supportive treatment may include anti-emetics, antidiarrheal medications, anti-pyretics, anti-histamines, analgesics, antibiotics, and others, such as blood products. Patients who experience indigestion or gastroesophageal reflux symptoms may be treated with Proton Pump Inhibitors (PPIs) as well as H2 blockers as clinically indicated.

Blood products transfusions will be administered according to institutional guidelines. Plasma products, antibiotic and antifungal therapy will be administered on as needed on an individual case basis. Hematopoetic growth factors will be permitted for the management of anemia and/or neutropenia per ASCO guidelines. Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician.

7.0 Clinical and Laboratory Evaluations

Cycle	**Screen**	**1a**	**1b**	**2a**	**2b**	**3a**	**3b**	**Follow Up** (Every 6 month ± 1 month)	**Withdrawal of study treatment[g]**
Day[d]	**0**	**1**	**15**	**1**	**15**	**1**	**15**		
Informed consent	X								
Inclusion/exclusion criteria	X								
Medical history (including hormone functional status)	X	X		X		X			X
Physical examination	X	X		X		X			X
Performance Status	X	X		X		X		X[e]	X
Vital signs	X	X	X	X	X	X	X		X
Hematology/chemistry	X	X	X	X	X	X	X		X
Urinalysis or dipstick[b]	X	X		X		X			X
Biomarkers[c]	X	X		X		X			X
Pregnancy test	X								

Cycle	Screen	1a	1b	2a	2b	3a	3b	Follow Up (Every 6 month ± 1 month)	Withdrawal of study treatment[g]
Day[d]	**0**	**1**	**15**	**1**	**15**	**1**	**15**		
RECIST	X[a]					X[a]		X[f]	X[a]
Tolerability/AE reporting		X		X		X			X
Concurrent medication (Somatostatin analogue only) [h]	X	X		X		X			X
Bevacizumab (d1 + 15)		X	X	X	X	X	X		
Capecitabine (d1-14)		X		X		X			
Temozolomide (d10-14)		X		X		X			

a- Measurement of tumor will be done at baseline, every 3 cycles (end of cycle 3, 6, 9, etc.) and at withdrawal of study treatment
b- Urinalysis or dipstick obtained at screening and at least every 4 weeks. See section 6.1.3 for further details.
c- Sampling of serum for chromogranin A levels will be done on the first day of each cycle, other hormone markers may be checked at the investigator's discretion.
d- Patients may be seen within a +/- 7 -days window of the assigned study visit.
e- Survival follow up can be done by phone call or clinic visit
f- Till disease progression
g- If patient doesn't want to be followed up.
h- Start and stop dates and dose of somatostatin analogue (SSA) should be recorded. SSAs include short and long-acting Octreotide and Lanreotide.

7.1 Pre-Treatment Evaluations

- Screening visit to occur ≤ 14 days prior to start date.
- Vital signs, including blood pressure
- Medical history, physical exam, and assessment of performance status
- Functional status should be recorded as "Yes or No." Functional status is defined as elevated hormone biomarker with symptoms attributable to that hormone elevation (i.e. flushing or diarrhea associated with elevated serotonin or urine 5HIAA). To be determined by treating physician.
- Blood: Complete blood count with differential, comprehensive metabolic panel, Chromogranin A, other neuroendocrine markers at the investigator's discretion, and serum banked for future studies (banked serum is mandatory).
- Urine:
  - Urinanalysis (pH, specific gravity, glucose, protein, ketones and blood) OR urine dipstick are allowed. Patients with 0, trace, or 1+ protein are eligible to enroll, if >= 2+ must check 24h urine protein and must be < 1g to start study.
  - Pregnancy test if female
- Tissue: MGMT deficiency (optional depending on availability, centrally tested at Stanford). See below in section 7.3 for details.
- Imaging:
  - Radiographic imaging, multi-phasic CT or MRI preferred, of measurable disease for assessment by RECIST criteria (standard clinical care). This must be done within 30 days of starting on study.

- CT Perfusion will be performed at baseline as a correlative study (Optional)

7.2 Evaluations During Treatment

On the first day of each cycle:

- Medical history, physical exam, and assessment of performance status
- Vital signs, including blood pressure
- Blood: Complete blood count with differential, comprehensive metabolic panel, Chromogranin A, and other neuroendocrine markers at the investigator's discretion within 48 hours before treatment.
- Chromogranin A and other neuroendocrine markers need not be repeated if it is done within last 3 weeks in case of delayed cycle or chemotherapy break.

* Urine: Urinanalysis (pH, specific gravity, glucose, protein, ketones and blood) OR urine dipstick are allowed. Patients with 0, trace, or 1+ protein are eligible to get treated. For the first occurrence of a 2+ value, 24-hour urine confirmation is required. If the confirming 24-hour urine is <2g/24h, subsequent 2+ urinalysis or dipstick values for that patient are acceptable.

- Imaging:
  - Multi-phasic CT or MRI scans with measurement of target lesions by RECIST criteria will be done at the conclusion of every 3 cycles
  - CT Perfusion will be performed after 2 wks and after 3 cycles as a correlative study. (Optional)

7.3 Post-Treatment Evaluations

Upon patient withdrawal from study, every effort will be undertaken to obtain the following (unless done within 4 weeks of study withdrawal):

- Medical history, physical exam, and assessment of performance status
- Vital signs, including blood pressure
- Blood: Complete blood count with differential, comprehensive metabolic panel, Chromogranin A, and other neuroendocrine markers at the investigator's discretion.
- Imaging:
  - Multiphasic CT or MRI scans with measurement of target lesions by RECIST criteria and CT Perfusion (OPTIONAL) as a correlative study will be performed if not done within 4 weeks prior to withdrawal from study.
  - Additional imaging will be at the investigator's discretion per standard of care.

7.4 Correlative Tissue/Blood Studies

Representative tumor tissue samples will be used in the studies described below. The results of these studies are for the purposes of the trial only and will not be returned to the site or reported to the patient. Tissue for MGMT testing will be optional depending on availability and will not be an eligibility requirement.

Priority of tissue use:
1. MGMT status by IHC
2. MGMT status by promoter methylation

Evaluation of MGMT status by IHC
Mouse monoclonal antibody to MGMT will be used (1:25 dilution; clone MT 3.1; Lab Vision), a biotinylated secondary antibody (mouse IgG), and then avidin-horseradish peroxidase (Vectastain Elite ABC Kit; Vector Laboratories) according to the manufacturer's instructions. Immunohistochemical MGMT expression will be scored as either ''intact'' or ''deficient'' in tumor cells using a prospective classification scheme. Tumors will be scored as ''intact'' when there is nuclear staining for MGMT in any tumor cells. Tumors will be scored as ''deficient'' when there is a complete absence of nuclear staining for MGMT in all tumor cells. Non-neoplastic cells (lymphocytes, stromal cells, and endothelial cells) served as an internal positive control in all tissue sections. We will additionally use an external tissue array control slide with known negative tumor. The assay will be performed in a CLIA certified lab under the direction of Teri Longacre, MD at Stanford University.

Evaluation of MGMT status by promoter methylation
DNA is purified from formalin-fixed paraffin embedded and then treated with bisulfite. Bisulfite treatment chemically converts unmethylated cytosines to uracil but does not affect methylated cytosine. Two PCR reactions are then performed using primers corresponding to bisulfite modified (unmethylated) or unmodified (methylated) MGMT promoter sequence. The products of the PCR reaction are analyzed by agarose gel electrophoresis. Methylation-specific PCR performed on paraffin-embedded tissue specimens is dependent on tissue quality and quantity. It is important that there is little tissue necrosis since amplification could otherwise be compromised. It is to be expected to frequently see amplification of both methylated and unmethylated MGMT promoter sequences in the same specimen, which likely represents heterogeneity among tumor cells and/or the presence in the specimen of non-neoplastic cells. Presence of promoter methylation, which causes epigenetic silencing of the MGMT gene, a DNA repair gene on chromosome 10q26, is a positive predictive factor for chemotherapeutic response to alkylating agents. The assay will be performed in a CLIA certified lab under the direction of Iris Schrijver M.D at Stanford University.

Corrleative Specimen Submission Requirements
Diagnostic material from previously collected tissue (core biopsy or surgical specimen preferred over FNA) must be submitted for optional laboratory research studies. Peripheral blood is to be submitted from consenting patients for future research studies. The IRB-approved consent must allow patients the option to provide specimens to for use in the optional laboratory studies and for undefined future research.

Specimen Preparation Guidelines
Tissue Samples
The following materials are to be submitted:

- One representative diagnostic formalin-fixed paraffin-embedded tumor block, core biopsy or surgical specimen preferred.
- NOTE: If a block is unavailable for submission, submit the following:
    - For MGMT IHC: 3 unstained slides, 4 microns thick
    - For MGMT promoter methylation: 3 unstained slides, 20 microns thick

Peripheral Blood, ACD or EDTA

- Blood specimens will be collected during routine care on cycle 1 day 1 using three tubes, for whole blood (6 cc purple top), serum (6cc red top) and plasma (6 cc purple top)
- All blood samples will be processed within 3 to 4 hours of collection. The serum sample should be kept at room temperature for at least 30 minutes prior to centrifugation.
- For serum and plasma, samples will be spun in a centrifuge for 15 minutes at 3000 rpm at room temperature. After spinning plasma will be pipetted into five storage tubes of one milliliter each and serum will be pipetted into two storage tubes of one milliliter each. One tube of whole blood will be stored without processing.
- These samples may be stored at the individual sites until the time of analysis in a -80C freezer per institutional protocols at Stanford, UCSF and Moffitt.

Pathology Contact information
Tissue samples should be labeled:
“For Kunz Ph II Trial Tem/Cape/Bev central MGMT review”

Tissue samples should be mailed to:
Pamela Kunz, MD
Stanford Cancer Institute
875 Blake Wilbur Drive
Stanford, CA 94305-5826
pkunz@stanford.edu

Pathology samples will be distributed by Dr. Kunz and her team to the appropriate investigators as follows to:

For MGMT immunohistochemistry:
Teri Longacre, M.D.
Professor of Pathology
Stanford University School of Medicine
Department of Pathology
300 Pasteur Drive
Stanford, CA 94305
Phone [redacted]
Email: [redacted]

For MGMT promoter methylation:

Iris Schrijver M.D.
Associate Professor of Pathology
Stanford University School of Medicine
Department of Pathology / Molecular Pathology
300 Pasteur Drive
Stanford, CA 94305-5627
Phone:
Fax:
Email:

8.0 Subject Discontinuation

Patients will continue on treatment until one of the following occurs:

1. Patient chooses to withdraw from study
2. Unacceptable toxicity occurs
3. Evidence of progressive disease by RECIST criteria

Specific reasons for discontinuation are listed below:

1. Patient removes consent
2. Completion of protocol treatment
3. Patient relapses or progresses to a point that additional or alternative therapy is indicated
4. The patient may withdraw from the study at any time for any reason.
5. Patient is now excluded
6. Patient fails to meet scheduled clinical visits leading to a sufficiently incomplete dataset for analysis
7. Patient is diagnosed with a new tumor requiring treatment
8. The patient has a clinically significant treatment adverse event as determined by the Principal Investigator.
9. The development of circumstances which prevent study evaluations/visits
10. The patient requires a dose level of <100 mg/m2/day for 5 days for TEMODAR.
11. Evidence of disease progression prior to completion of 3 cycles
12. Patient is non-compliant with study medication
13. Grade 4 hypertension or Grade 3 hypertension not controlled with medication
14. Nephrotic syndrome
15. Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage

16. 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)
17. Any grade arterial thromboembolic event
18. Grade 4 congestive heart failure
19. Gastrointestinal perforation
20. Tracheoesophageal fistula (any grade) or Grade 4 fistula
21. Grade 3 or greater bowel obstruction that has not fully recovered despite medical or surgical intervention
22. Wound dehiscence requiring medical or surgical intervention
23. Unwillingness or inability of subject to comply with study requirements
24. Determination by the investigator that it is no longer safe for the subject to continue therapy
25. All Grade 4 events thought to be related to bevacizumab by the investigator
26. Becomes pregnant
27. Withdrawal of consent
28. Development of a serious intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
29. Progressive disease

NOTE: Patients who have an ongoing 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.

9.0 Study Follow Up

After study treatment discontinued patients will be followed every 6 months till death for disease progression and survival. (See section 7.0) Discontinuation of the study will be considered after review of the data by the DSMC for any of the following events:

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

10.0 Statistical Methods

10.1 Determination of Sample size

A sample size of 30 patients would give 80% power to reject the null RR of 40% if the true response rate (RR) is 65% or higher. The null hypothesis is based on a prospective phase II study conducted by Kulke, et al evaluating the efficacy of temozolomide and thalidomide[1]. In this study, 29 patients with mixed metastatic NETs were treated with temozolomide 150 mg/m^2 for 7 days every other week and thalidomide at doses of 50-400 mg daily. The overall radiographic response was 25% (45% in patients with

pancreatic NETs). The alternative hypothesis is based on the more recent retrospective study in patients with pancreatic NETs reported by Strosberg, et al in which 30 patients were treated with capecitabine (750mg/m^2 twice daily, days 1-14) and temozolomide (200 mg/m^2 once daily, days 10-14) every 28 days; the RR was 70%[6]. RR is defined as the proportion of patients with complete response + partial response (CR+PR) based on a patient's best response.

The study will be stopped if there are excessive toxicities associated with the study regimen. An interim analysis for safety will be performed after the first 10 patients have been treated. All patients receiving at least one dose of protocol therapy will be included in the analyses. Specifically, we will stop the study and re-evaluate the approach if it is determined that ≥3 of the first 10 patients experience grade 3/4 non-hematologic treatment-related adverse events despite adequate supportive care (excluding alopecia), or grade 4 hematologic treatment-related adverse events despite adequate supportive care, or other excessive toxicity resulting in death or removal from study (as outlined in Section 6.0). The patients included in these analyses will be followed without stopping study accrual.

10.2 Planned Efficacy Evaluations

Primary Efficacy Variables

- RR and AEs

Secondary Efficacy Variables

- PFS and OS
- Biomarkers
- MGMT
- CT perfusion (if performed)

Efficacy Assessment using Response Evaluation Criteria in Solid Tumors Guideline (RECIST v 1.1)[29]

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

Measurable:

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

scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable:

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

Specifications by methods of measurements

Measurement of lesions:

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

Method of assessment

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

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

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

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

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

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

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

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

Tumor response evaluation

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

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

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

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

Response criteria

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

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

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

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

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

Time point response: patients with target (+/- non-target lesions) disease

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

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

Definitions of Other Efficacy Markers

Radiographic Response Rate (RR): The proportion of patients with complete response + partial response (CR+PR) based on a patient's best response.

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

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

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

NOTE: Imaging will be performed and reviewed at the separate sites; a central radiology review will not be performed.

10.3 Plan of analysis

The proportion of RR (CR+PR) will be estimated along with a one-sided lower 95% exact confidence bound to allow an informal assessment of the null hypothesis (RR=40%) based on binomial probabilities; assessment will be regarded as informal since we do not expect to be able to adjust for differences in clinical and demographic in the comparator study. Proportions will be estimated along with 95% exact confidence intervals. Time to

event data will be evaluated using Kaplan-Meier estimates with 95% confidence intervals at multiples of 12 months based on Greenwood's formula with a log transform. Confidence intervals for median times to event, if relevant, will be constructed using the method of Brookmeyer and Crowley. Biomarkers will be summarized using medians and interquartile ranges; changes in biomarkers will be assessed using Wilcoxon's signed rank test. Adverse events will be tabulated by organ system and severity. Patient clinical and demographic characteristics will be reported with the appropriate summary statistic (mean, range, proportion etc.) Progression-free survival (PFS) and overall survival (OS) will be evaluated using Kaplan-Meier analysis. For PFS analyses, patients will be censored at time last known alive if no progression has occurred. De-identified patient data will be used for all analyses.

11.0 Safety Reporting of Adverse Events

11.1 Genentech-specific Safety Reporting (for both capecitabine and bevacizumab)

Assessment of Safety

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to capecitabine or bevacizumab, all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with advanced pancreatic neuroendocrine tumors that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Methods and Timing for Assessing AND Recording Safety variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the {study drug} (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the {study drug}, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the {study drug}; and/or the AE abates or resolves upon discontinuation of the {study drug} or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

Procedures for Eliciting, Recording, and Reporting Adverse Events

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

- “How have you felt since your last clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 11.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only

if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.
-

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the {study drug} should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior {study drug} exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. SAE Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(XXX-xxx-xxxx
OR

(xxx) xxx-xxxx

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to capecitabine or bevacizumab will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to capecitabine or bevacizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- Additional Reporting Requirements to Genentech include the following:
- Any reports of pregnancy following the start of administration with the capecitabine or bevacizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded, at most, on a quarterly report to Genentech.

Note: Investigators should also report events to their IRB as required.

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:

- 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 patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient 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 patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/medwatch/getforms.html

Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The 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 capecitabine or bevacizumab. An unexpected adverse event is one that is not already described in the capecitabine or bevacizumab Investigator Brochures. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of capecitabine or bevacizumab .An unexpected adverse event is one that is not already described in the capecitabine or bevacizumab investigator brochures.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (

AND to the Site IRB:

Stanford IRB / Research Compliance Office
1501 S. California Avenue, [Mail Code: 5579]
Palo Alto, CA 94304
Fax: x

AND to Stanford (for subsites UCSF and Moffitt):

Study Coordination Center/Principal Investigator
Pamela Kunz, MD
Stanford Cancer Center
875 Blake Wilbur Drive
Stanford, CA 94305-5826
x
pkunz@stanford.edu

For questions related to safety reporting, please contact Genentech Drug Safety:

x

IND Annual Reports
Copies to Genentech:

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

x

Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Avastin Protocols
Email: avastin-gsur@gene.com
Fax : [redacted]

11.2 Merck Safety Reporting

Follow same AE and SAE definitions as above.

For Merck, all SAEs should be recorded on a MedWatch 3500a Form and faxed to:

Merck (Attn: Worldwide Product Safety; FAX 215 993-1220) must be provided with copies of all serious adverse experiences, within two working days regardless of drug relationship. Any pregnancy occurring in association with use of a Merck Product must also be reported to Merck (Attn: Worldwide Product Safety; FAX x).

AND:

Stanford IRB / Research Compliance Office
1501 S. California Avenue, [Mail Code: 5579]
Palo Alto, CA 94304
Fax [redacted]

AND (for subsites UCSF and Moffitt):

Study Coordination Center/Principal Investigator
Pamela Kunz, MD
Stanford Cancer Center
875 Blake Wilbur Drive
Stanford, CA 94305-5826
[redacted]
pkunz@stanford.edu

Merck follow-up period. Patients will be followed for 30 days after they have been taken off trial regardless of causality.

12.0 Retention of Records

Research data will be recorded on study-specific Case Report Forms (CRFs) using a unique patient number for each patient to assure patient confidentiality. Data from source documents are used to transcribe critical protocol data on CRFs. Source

documents are documents where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, quality of life assessments, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, X-rays, patient filed, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial.

Any publication or presentation will refer to patients by this number and not by name. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are maintained by a designated research coordinator and kept in a locked room with access restricted to personnel authorized by the Division of Clinical Research. A study-specific database will also use the unique patient number and will not include patient names. Access to the database will be restricted by electronic password protection and restricted access to computers (i.e., locked offices).

13.0 Data and Safety Monitoring Plan

Stanford Cancer Institute will be the coordinating institution. Ongoing trial oversight is carried out by the principal investigator, Dr. Pamela Kunz and her research staff. Adverse events will be reviewed in real time. Additionally, summaries of SAEs and AEs will be reviewed weekly at the Developmental Therapeutics Meeting and monthly with the subsites to discuss trends. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Stanford will perform twice yearly on site audits of source documents. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above. All investigators on the protocol have received formal training in the ethical conduct of human research. Institutional support of trial monitoring is provided in accordance with the Stanford University Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, the Stanford Research Trials Office coordinates monitoring for data accuracy and compliance by consultants, contract research organizations, or Stanford employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits. In addition, protocols are reviewed at least annually by the Data and Safety Monitoring Committee (DSMC) and the Institutional Review Board (IRB). The Stanford IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of the IRB is necessary to continue the study. The trial will comply with the standard guidelines set forth by the regulatory committees of the Stanford (Scientific Review Committee, IRB, DSMC) and other state and federal guidelines.

To ensure trial-wide data and safety monitoring, the Principal Investigator will obtain copies of all local IRB approvals and will have the responsibility for receiving the information required for adverse event reporting and safety monitoring from outside sites, and disseminating that information to the appropriate Consortium committees. The

Principal investigator is responsible for establishing and carrying out procedures for assessing protocol compliance, data accuracy and completeness, and full and timely reporting of safety data at outside sites. Written agreements will be obtained from all participating sites acknowledging their responsibilities for data and adverse event reporting and agreement to provide records, files, case report forms or any other documents to verify compliance.

14.0 Ethical and Regulatory Considerations

General: Stanford will be the coordinating institution. As such, all Case Report Forms (CRFs) will be reviewed by Stanford research staff for compliance. Imaging will be reviewed separately at each site; a central review will not occur.

Institutional Review Board

In accordance with federal regulations (21 CFR 312.66), an Institutional Review Board (IRB) at Stanford that complies with regulations in 21 CFR 56 must review and approve this protocol and the informed consent form prior to initiation of the study.

Independent Ethics Committees/Institutional Review Board

This protocol and the informed consent will be approved by the Stanford IRB. The Principal Investigator is responsible for keeping the IRB advised of the progress of the study and of any changes made in the protocol prior to implementation. The Principal Investigator will also keep the IRB informed of any significant adverse reactions, and any protocol exceptions or deviations. Records of all study review and approval documents must be kept on file by the Principal Investigator and are subject to FDA inspection during or after completion of the study. The IRB will receive notification of the termination of the study.

Consent

The Principal Investigator or his designee must explain verbally and in writing the nature, duration, and purpose of the study and possible consequences of treatment. Patients must also be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. In accordance with federal regulations (21 CFR 50), all patients enrolled in the study must sign the IRB-approved consent form.

Clinical Trials Database and Results Registration

The principal investigator will register the clinical trial at www.clinicaltrials.gov, the US National Library of Medicine website prior to initiation of the study. This website provides regularly updated information about US government and privately supported clinical research in human volunteers. In addition, the investigator will make the results of the study publicly accessible by publication and by posting the results on www.clinicaltrials.gov.

Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety at weekly study group or site committee meetings where the results of each patient's data and status are discussed and the discussion is documented in the minutes. The discussion will include

any toxicity from temozolomide treatment including dose de-escalations if they were required. Quarterly summaries will be submitted to the DSMC for review. All AE's and SAE's from temozolomide would have been entered into the Stanford Comprehensive Cancer Center CTMS database. The study coordinator will keep a log of subject(s) temozolomide treatment.

Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator, Genentech or Merck, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study drugs must be returned to Genentech or Merck.

Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted after FHCRC IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. The investigator, Genentech and Merck will review informed consent documents prior to IRB/IEC submission.

Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Genentech and Merck, and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Genenteach, Merck and the regulatory authority(ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

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[Bevacizumab references provided as separate document on diskette]

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APPENDICES:
Appendix A: NCI Common Toxicity Criteria, v4.0 (website provided)
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix B: FDA MedWatch 3500a Form (website provided)
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

Appendix C: NYHA Guidelines (included)

Appendix D: Genentech Safety Reporting Cover Sheet (included)

ATTACHMENTS:
Attachment 1: Informed Consent Form (separate attachment)

APPENDIX C: NYHA Guidelines[30]

Class I (mild): no limitation is experienced in any activities; there are no symptoms from ordinary activities.

Class II (mild): slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.

Class III (moderate): marked limitation of any activity; the patient is comfortable only at rest.

Class IV (severe): any physical activity brings on discomfort and symptoms occur at rest.

APPENDIX D:

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: xxxxxxxxxx

Alternate Fax No: xxxxxxxxxxx

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	*[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]*
Follow-up Report Date	*[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]*

Subject Initials *(Enter a dash if patient has no middle name)*	*[INSERT investigational product name] - [INSERT investigational product name] - [INSERT investigational product name]*

SAE or Safety Reporting questions, contact Genentech Safety: (

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET