A PHASE II STUDY OF BEVACIZUMAB WITH CONCURRENT CAPECITABINE AND RADIATION FOLLOWED BY MAINTENANCE GEMCITABINE AND BEVACIZUMAB FOR LOCALLY ADVANCED PANCREATIC CANCER

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Bevacizumab (NSC 704865, IND 7921) will be supplied by the NCI

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0411

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SCHEMA

Capecitabine and Bevacizumab with Concurrent Radiation

R
Capecitabine: q 12 hours M-F on RT days

‡Bevacizumab: On day 1, 15, and 29 with chemoradiation

RT: 28 fractions over 5.5 weeks

CT evaluation for progression 3-4 weeks after the end of concurrent radiation

Then post-chemoradiation beginning 4-7 weeks after radiation completed

Maintenance Gemcitabine and Bevacizumab

Gemcitabine: Weekly for 3 weeks, then 1 week off, continuing until progression

‡Bevacizumab: Every 2 weeks, continuing until progression

‡Proton pump inhibitor (PPI) medications must be administered to all patients. See Section 9.2.1.
For Capecitabine, Bevacizumab, and Gemcitabine: See Section 7.0 for details.
RT: See Section 6.0 for details.

Patient Population: (See Section 3.0 for Eligibility)
Patients must have unresectable disease based on institutional standardized criteria of unresectability. There must be no evidence of metastatic disease in the major viscera and no peritoneal seeding or ascites. All malignant disease must be encompassable within a single irradiation field. Zubrod performance status 0-1.

Required Sample Size: 82
| Case # |  |  |
|--------|-----------------------------|
|        | RTOG Institution # _________ | RTOG ELIGIBILITY CHECKLIST (1/18/05)(3/8/05) | (page 1 of 3) |
| 1.     | (Y) Does the patient have a pathologically confirmed adenocarcinoma of the pancreas? |  |
| 2.     | (Y) Does the patient have unresectable disease based on your institution's standardized criteria of unresectability? |  |
| 3.     | (N) Is there evidence of metastatic disease in the major viscera, peritoneal seeding or ascites? |  |
| 4.     | (Y/N) Does the patient have biliary or gastroduodenal obstruction? |  |
|        | ______ (Y) If yes, does/will the patient have drainage or surgical bypass prior to beginning chemoradiation? |  |
| 5.     | (Y) Is all malignant disease encompassable within a single irradiation field? |  |
| 6.     | (Y) Does the patient have radiographically assessable disease? |  |
| 7.     | (N) Has the patient had prior radiation to the planned field? |  |
| 8.     | (N) Has the patient had prior chemotherapy for pancreatic cancer? |  |
| 9.     | (Y) Do the patient’s laboratory values meet the criteria in Section 3.1.9? |  |
| 10.    | (Y) Has the required CT/MRI of the abdomen and chest X-ray been performed within 4 weeks of study entry? |  |
| 11.    | (N) Does the patient have significant infection or other coexistent medical condition that would preclude protocol therapy? |  |
| 12.    | (N) Did the patient have a stroke within the previous 6 months? |  |
| 13.    | (N) Is the patient pregnant or lactating? |  |
| 14.    | (Y/N) Has the patient had prior malignancies, except for non-melanomatous skin cancers, or carcinoma in situ of the uterus, cervix, or bladder? |  |
|        | ______ (Y) If yes, has the patient been disease-free for ≥ 2 years? |  |
| 15.    | (Y) Is the patient’s Zubrod Performance Scale score 0-1? |  |
| 16.    | (Y) Has the patient’s baseline urine protein been measured? |  |
| 17.    | (Y/N) Is the patient’s baseline proteinuria ≥1+ or urine protein:creatinine ratio ≥ 1.0 ? |  |
|        | ______ (Y) If yes, has the patient undergone a 24-hour urine collection with the results demonstrating < 1000 mg of protein/24 hr? |  |
| 18.    | (N) Is there invasion of pancreatic cancer into the duodenum? |  |
| 19.    | (N) Does the patient require warfarin sodium for anticoagulation? |  |

(continued on next page)
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
11. Gender
12. Patient’s Country of Residence
13. Zip Code (U.S. Residents)
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Treatment Start Date
17. Medical Oncologist
18. Tissue/Blood kept for cancer research?
19. Tissue/Blood kept for medical research?
20. Allow contact for future research?

(Continued on the next page)
The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _______________________________ Date ______________________________
1.0 INTRODUCTION

1.1 Background and Preliminary Data
There are approximately 30,400 new cases of pancreatic carcinoma each year in the United States. The overall 5-year survival has remained constant at < 5%. Approximately half of all patients have locally advanced, unresectable disease at the time of initial diagnosis. Standard treatment for locally advanced disease is fluorouracil (5-FU) and external beam irradiation. The addition of 5-FU as radiosensitizing agent modestly increases local control and median survival, however, virtually all patients will eventually develop disease progression and death. More effective treatments are clearly needed.

1.2 Capecitabine and Radiation
Capecitabine is a novel fluoropyrimidine designed for oral administration. It is converted to the cytotoxic agent fluorouracil through a series of enzymatic steps in vivo. The final step in conversion to fluorouracil is by thymidine phosphorylase, which is found in higher levels in tumor cells than in normal tissues. This increased rate of conversion to the active cytotoxic agent at the tumor site minimizes the exposure of normal body tissues to systemic 5-FU. The use of capecitabine allows prolonged administration of a fluoropyrimidine without the use of indwelling catheters required for infusional 5-FU.

Capecitabine is well tolerated with radiotherapy. For example in a phase I trial in patients with rectal cancer, capecitabine was administered continuously (7 days per week) throughout a 38 day course of radiotherapy (50.4 Gy in 28 fractions). Therapy was well tolerated. The recommended dose was 825 mg/m² PO BID and the dose limiting adverse event was hand foot syndrome. At M.D. Anderson, capecitabine has been used as a substitute for protracted venous infusion 5-FU in over 100 patients with GI malignancies receiving radiotherapy and has been very well tolerated. M.D Anderson has used 900 mg/m² on a 5-day schedule (Monday-Friday with radiotherapy) and the only significant adverse event has been Grade 3 hand foot syndrome in < 10% of patients (Crane unpublished data).

1.3 Bevacizumab, capecitabine and radiation in pancreatic cancer (7/29/05)
New blood vessel growth is required for solid tumors to expand beyond a volume of 1-2 mm³. Immunohistochemical analysis of tumor sections from the margins of growing tumors show a preponderance of blood vessels, irrespective of tumor type. Tumors that have undergone neovascularization not only can enter a phase of rapid growth but also demonstrate increased metastatic potential. Recent studies relating the angiogenic phenotype and survival in people have shown that the number of microvessels in a primary tumor has prognostic significance in several tumor types carcinomas, including pancreatic cancer.

Recognition that angiogenesis is essential to the growth of solid tumors has led to identification of angiogenic factors responsible for stimulating new blood vessel formation. Of the identified angiogenic factors, vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is the most potent and specific and has been identified as a crucial regulator of both normal and pathologic angiogenesis. VEGF produces a number of biologic effects, including endothelial cell mitogenesis and migration, induction of proteinases leading to remodeling of the extracellular matrix, increased vascular permeability, and maintenance of survival for newly formed blood vessels. Increased levels of VEGF expression has been found in most human tumors examined to date including pancreatic cancer.

Inhibition of VEGF using an anti-VEGF monoclonal antibody blocks the growth of a number of human cancer cell lines in nude mice. The human cancers represented by these cell lines that are growth-inhibited by anti-VEGF antibody include non–small cell lung cancer (Calu-6), colorectal cancer (LS174T, HM-7, LSLiM6), breast cancer (MCF-7), prostate cancer (D-145), head and neck cancer (KB) and ovarian cancer (SK-OV-3). In addition, the combination of anti-VEGF antibody and chemotherapy in nude mice injected with human cancer xenografts results in an increased antitumor effect compared with antibody or chemotherapy treatment alone.

Bevacizumab (rhuMAb VEGF) is a humanized monoclonal antibody to VEGF. Hurvitz et al reported a dramatic survival benefit in a randomized study for patients with metastatic colon cancer randomized to irinotecan/5-fluorouracil/leucovorin (IFL) with bevacizumab or placebo.
Bevacizumab was shown to extend survival significantly - the first validation in a phase III clinical trial of an antiangiogenic therapy to treat human cancer. Survival was increased from 15.6 months with IFL, to 20.3 months with IFL and bevacizumab (p=0.00004). Bevacizumab was generally well tolerated. There appeared to be an increase in GI perforations from the addition of bevacizumab. There were 6 perforations (0.8%) in the IFL/bevacizumab arm and no perforations in the IFL control arm. In one patient, the perforation resulted in death. Other increases in grade 3 or 4 toxicities were hypertension (12% vs 2%), intra-abdominal thrombosis (3% vs 1%) and deep vein thrombosis (9% vs 5%) in the bevacizumab/IFL arm versus the control arm, respectively. There also was an increase in grade 4 bleeding (0.8% vs 0%). Furthermore, in an analysis of five randomized bevacizumab trials, there was a 2 fold higher risk of arterial thrombotic events with bevacizumab.

Preliminary data presented by Kinder at the ASCO GI Symposium in January 2004 suggests that bevacizumab may also be useful in pancreatic cancer. A 26% response rate and 9-month median survival was reported with bevacizumab and gemcitabine for patients with metastatic pancreatic cancer.

The MD Anderson Cancer center is completing a phase I trial of bevacizumab/capecitabine and concurrent radiation for patients with locally advanced pancreatic cancer. Bevacizumab (5 mg/kg IV) was administered to all patients 2 weeks prior to the start of XRT (50.4 Gy treating the primary tumor and gross adenopathy), then every 2 weeks thereafter (2.5 mg/kg, n = 12; 5 mg/kg n = 12; then 7.5 mg/kg, n = 6). Capecitabine was administered continuously with radiotherapy on days 14-52 (650 mg/m² PO BID for the first six patients, then 825 mg/m² PO BID for the remaining patients. Patients with stable or responding disease were offered maintenance bevacizumab (5 mg/kg IV q 2 wks) until progression. The worst acute gastrointestinal toxicity during chemoradiation was Grade 2 in 20/47 (43%) and Grade 3 in 2/47 (4.3%) patients treated. These two patients were the only patients that required hospitalization during chemoradiation. Eleven patients (23%) developed Grade 2 hand and foot syndrome and 4 patients developed uncomplicated Grade 3 hematologic toxicity. In an effort to cut down the Grade 2 toxicity rate, the weekend doses of Capecitabine were dropped for the last 12 patients. In that group, only 3 of 12 patients experienced Grade 2 toxicity and none experienced grade 3 toxicity.

### Table 1. Worst gastrointestinal toxicity*

<table>
<thead>
<tr>
<th>Level</th>
<th>Bevacizumab (mg/kg/2wks)</th>
<th>Capecitabine (mg/m² BID)</th>
<th>Dose</th>
<th>N</th>
<th>Nausea/Vomiting/Anorexia</th>
<th>Gastritis</th>
<th>Diarrhea</th>
<th>Dehydration</th>
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<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>650</td>
<td>2</td>
<td>6</td>
<td>G2</td>
<td>G3</td>
<td>G2</td>
<td>G3</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>825</td>
<td>2</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>1®</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>825</td>
<td>3</td>
<td>12</td>
<td>2</td>
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<td>1</td>
</tr>
<tr>
<td>4</td>
<td>7.5</td>
<td>825</td>
<td>4</td>
<td>11</td>
<td>3®</td>
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<td>1</td>
<td>1®</td>
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<tr>
<td>5</td>
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<td>825®</td>
<td>5</td>
<td>12</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
<td>47</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Summary: 20/47 (43%) Grade 2 and 2/47 (4.3%) Grade 3 gastrointestinal events

* All grade 3 or greater adverse events that occurred are listed.
* (National Cancer Institute Common Toxicity Criteria, Version 3)
® Both patients with grade 3 toxicity required admission to the hospital for supportive care
# One patient was taken off-study after first dose of bevacizumab and not included in analysis
^ Capecitabine was given during days of radiation only at level 5.

**Abbreviations:** BID = twice daily; N = number of patients; XRT = radiation; G = grade

### 1.4 Adverse Events Possibly Attributable to Bevacizumab (7/29/05) (4/21/06)

Four of the first 30 patients had Grade 3 or greater perforation or duodenal ulceration with bleeding in the treatment field after the completion of chemoradiation. After recognizing that these events occurred in patients with apparent tumor invasion of the duodenal mucosa, care was taken to exclude these patients for the remainder of the study. There were no further bleeding events among the final 18 patients accrued (Table 2). Three of these patients had bleeding arising from ulcerated mucosa adjacent to the tumor within the radiation field 3, 10, and 20 weeks after the completion of chemoradiation. After a near-complete response to therapy, the first patient subsequently had an ulceration in the duodenal mucosa adjacent to the tumor and
bleeding requiring transfusion and endoscopic coagulation. The ulcer healed with supportive care. The second patient developed a bleeding duodenal ulcer near the tumor site that stabilized with discontinuation of bevacizumab and transfusion. The third patient had cavitation of the tumor, with the development of a fistula between the tumor and the third portion of the duodenum at the time of the first follow-up CT scan to evaluate response to therapy. The clinical manifestation of this was epigastric pain that lasted for 8 weeks after chemoradiation.

Upon careful retrospective review of the pretreatment imaging, a small fistulous connection between the tumor and the third portion of the duodenum was detected. The patient was not started on bevacizumab again until his pain resolved 10 weeks after therapy. The day after his first dose of bevacizumab, he had coffee ground emesis. Endoscopic evaluation revealed a necrotic, bleeding tumor mass involving the third portion of the duodenum. The bleeding could not be controlled in spite of attempted endoscopic laser and intra-arterial tumor embolization. The patient decided to forego further supportive care and transfusion, and died 2 weeks later at home. Two additional patients had grade 3 bleeding episodes at sites remote from the tumor and outside of the radiation field. One patient with a remote history of a non-muscle-invading bladder cancer had bleeding from the bladder mucosa one week after the first dose of bevacizumab. The bleeding was permanently controlled after endoscopic laser coagulation. This was the only patient to have a dose of bevacizumab withheld during chemoradiation (the second of four doses). Another patient, after receiving 12.5 months of bevacizumab after chemoradiation, had bleeding arising in the small bowel mucosa outside of the irradiated volume. The bleeding was successfully controlled with intra-arterial embolization, and bevacizumab was discontinued. The final patient had a grade 3 contained perforation of the duodenum immediately adjacent to the primary tumor, and fluid collection was seen on CT 10 weeks after the completion of chemoradiation. A transhepatic catheter was placed and bilious fluid was successfully drained percutaneously. She was discharged from the hospital after four days on oral antibiotics and pain medication.

Other adverse events of note included one patient who had a rapid onset of severe knee pain with edema during chemoradiation and bevacizumab. He had a history of pseudogout and very similar episodes. Although his pain was severe enough to limit ambulation, this event resolved spontaneously in 10 days with no interruption of therapy. Two patients had tonic-clonic seizure episodes during chemoradiation possibly related to bevacizumab. Head CT revealed no evidence of metastasis, hemorrhage, or infarction in either patient and seizure activity did not recur without the use of anticonvulsant therapy. Five patients (17%) had grade 1 proteinuria.

**Table 2: Toxicity possibly related to bevacizumab**

<table>
<thead>
<tr>
<th>Level</th>
<th>Dose (BEV mg/kg/2 wk)</th>
<th>Dose (CAP mg/m² BID)</th>
<th>N</th>
<th>GI Perforation</th>
<th>Ulcer/Fistula/Bleeding (within XRT field)</th>
<th>Bleeding (outside XRT field)</th>
<th>Hypertension</th>
<th>Seizures</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>650</td>
<td>6</td>
<td>-</td>
<td>G3 G2 G3 G5</td>
<td>G3 G2 G3</td>
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<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

All grade 3 or greater adverse events that occurred are listed;
* (National Cancer Institute Common Toxicity Criteria, Version 3);
# Bleeding occurred that required blood transfusion, embolization, or coagulation
^ Perforation related to acute appendicitis after one dose of bevacizumab in one patient and at the tumor site after the completion of chemoradiation in the other patient
@ Capecitabine was given during days of radiation only at level 5
Abbreviations: N = number of patients; XRT = radiotherapy; DVT = deep venous thrombosis; G = toxicity grade; BEV = bevacizumab; CAP = capecitabine
Nine of 46 evaluable patients (20%) achieved a partial radiographic response, including a 6/12 at the 5-mg/kg level. Only 7/47 (15%) patients have experienced objective local tumor progression (both after 5 months). Four patients have safely undergone pancreaticoduodenectomy (all with greater than 50% treatment effect seen in the pathologic specimen).

The MD Anderson study demonstrates that the addition of concurrent anti-VEGF therapy did not significantly increase the acute toxicity of a relatively well-tolerated chemoradiation regimen, but was associated with a small number of grade 3 or greater subacute mucosal adverse events (ulceration, fistula, bleeding and perforation) and late mucosal bleeding events. To potentially reduce mucosal toxicity, patients with known duodenal invasion will be ineligible for this RTOG trial. The 50% radiographic partial response rate at the 5-mg/kg levels, and low rate of radiographic local progression make the further study of bevacizumab with radiotherapy of considerable interest.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrated vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

2.0 OBJECTIVES
2.1 Primary Objective
2.1.1 The primary goal of this study is to compare overall survival at one year to a historical control for bevacizumab combined with capecitabine and concurrent radiation followed by maintenance gemcitabine and bevacizumab.

2.2 Secondary Objectives
2.2.1 To evaluate the frequency of unacceptable serious adverse events and unacceptable adverse events as defined in section 13.1.2.
2.2.2 To evaluate response rate and progression-free survival for this treatment regimen.

3.0 PATIENT SELECTION
3.1 Conditions for Patient Eligibility
3.1.1 Pathologically confirmed localized unresectable adenocarcinoma of the pancreas.
3.1.2 Patients must have unresectable disease based on institutional standardized criteria of unresectability.
3.1.3 Patients with biliary or gastroduodenal obstruction must have drainage or surgical bypass prior to starting chemoradiation
3.1.4 Patients who received chemotherapy > 2 years ago for malignancies other than pancreatic cancer are eligible, provided that chemotherapy was completed > 2 years ago and that there is no evidence of the second malignancy at the time of study entry.
3.1.5 All malignant disease must be encompassable within a single irradiation field
3.1.6 All patients must have radiographically assessable disease
3.1.7 Zubrod performance status 0-1
3.1.8 Age ≥ 18
3.1.9 Required entry laboratory parameters within 14 days of study entry: granulocytes ≥ 1500/µl; platelet count ≥ 100,000/µl; bilirubin < 2.0 mg/dL; ALT < 3 x upper limit of normal; INR ≤ 1.5; calculated creatinine clearance > 50 ml/min using Cockcroft-Gault formula: (7/29/06) (4/21/06)

CrCl male = (140 – age) x (wt. as kg) / (Serum Cr) x 72
CrCl female = 0.85 x (CrCl male)
3.1.10 Urine protein should be screened by dipstick or urine analysis. For proteinuria > 1+ or urine protein:creatinine ratio > 1.0, 24-hour urine protein should be obtained and the level should be < 1000 mg for patient enrollment.

3.1.11 Required CT/MRI of abdomen, and chest X-ray within 4 weeks of study entry

3.1.12 Negative blood pregnancy test within 7 days of the first day of study entry for women of childbearing potential.

3.1.13 Patients taking sorivudine or brivudine A (anti-virals) must be off of these drugs for 4 weeks. Patients taking cimetidine (e.g., Tagamet) must have this drug discontinued 30 days prior to the start of treatment. Ranitidine (e.g., Zantac) or a drug from another anti-ulcer class can be substituted for cimetidine if necessary.

3.1.14 Signed study-specific consent form prior to study entry

3.2 Conditions for Patient Ineligibility (10/20/05)

3.2.1 Evidence of duodenal invasion on CT scan or evidence of gastric outlet obstruction.

3.2.2 Evidence of metastatic disease in the major viscera or peritoneal seeding or ascites.

3.2.3 Previous irradiation to the planned field; previous chemotherapy for pancreatic cancer

3.2.4 Malignancy (within the past two years) except non-melanomatus skin cancer or carcinoma in situ of the cervix, uterus, or bladder

3.2.5 Pregnant, nursing, or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.6 Clinically significant cardiac disease (e.g., uncontrolled hypertension [blood pressure of >160/90 mmHg on medication], history of myocardial infarction within 6 months,), New York Heart Association (NYHA) Class II or greater congestive heart failure (see Appendix IV), unstable symptomatic arrhythmia requiring medication (subjects with chronic atrial arrhythmia, i.e., atrial fibrillation or paroxysmal supraventricular tachycardia) are not eligible. Patients with an atrial arrhythmia must have this condition well controlled on stable medication. Patients with current or recent (within 6 months) unstable angina are also not eligible.

3.2.7 Evidence of bleeding diathesis or coagulopathy, INR > 1.5

3.2.8 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to start of treatment, or anticipation of need for major surgical procedure during the course of the study; fine needle aspirations or core biopsies within 7 days prior to start of treatment

3.2.9 Serious, nonhealing wound, ulcer, or current healing fracture

3.2.10 History of aneurysms, transient ischemic attacks, and arteriovenous malformations

3.2.11 Patients who have had an organ transplant

3.2.12 Patients who require the use of warfarin sodium during chemoradiation are not eligible due to the interaction between warfarin sodium and capecitabine, which could lead to unexpected elevation in the INR. This could further predispose patients to bleeding while on bevacizumab. Warfarin sodium may be used beginning 2 weeks after chemoradiation is completed. Low molecular weight heparin is allowed at prophylactic dosages at any time during this protocol. (7/29/05)

3.2.13 Patients with recent (6 months) arterial thromboembolic events, including transient ischemic attack (TIA), cerebrovascular accident (CVA), or clinically significant peripheral artery disease should also be excluded.

3.2.14 Significant infection or other coexistent medical condition that would preclude protocol therapy

3.2.15 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.2.16 Patients with a history of a gastrointestinal fistula or perforation.

3.2.17 Patients with known hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies.

3.2.18 Known or suspected dihydropyrimidine dehydrogenase (DPD) deficiency. (7/29/05)

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT

(See evaluations in Section 3.0)

4.1 CBC, BUN, Na, K, AST, glucose, total protein, and albumin should be performed within 14 days of study entry and CA 19-9 within 21 days of study entry.

5.0 REGISTRATION PROCEDURES (7/29/05) (11/29/05)

5.1 Online Registration

Patients must be registered via the web only after eligibility criteria are met.
Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- The institution must complete the Password Authorization Form at http://www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, as discussed in Section 5.2.

5.2 Dial-in Registration

Patients can be registered only after eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY Note: Intensity Modulated RT (IMRT) Is Not Allowed

6.1 Dose Specifications

6.1.1 Primary Tumor and Regional Lymphatic Target (10/20/05)

All patients will be treated with the same radiotherapy technique. The primary tumor and any clinically enlarged lymph nodes will be treated with a block margin as referenced in Section 6.4.1.1. Total dose will be prescribed to the 95% and will be 50.4 Gy in 28 fractions over 5.5 weeks (1.8 Gy/1 day) with a 4-field technique. Beam weighting will be optimized to match the doses specified in Section 6.5.1.1.

6.2 Technical Factors

6.3 Localization, Simulation, and Immobilization

Simulation will be done with the patient in the supine "arms up" position using a CT-simulator.

6.4 Treatment Planning/Target Volumes

Three-dimensional treatment planning is required.

6.4.1 Target Volumes

6.4.1.1 Gross tumor volume (GTV): (10/20/05) The gross primary tumor and any lymph nodes enlarged over 1 cm is defined during simulation using contrast given during CT or MRI.
Clinical target volume (CTV): Regional lymph nodes will not be targeted. Because only the GTV will be treated, the GTV = the CTV.

Treatment field: A 2-cm block margin in the anterior, posterior, and lateral directions will be used. A 3-cm block margin in the cranial and caudal dimension will be used. The GTV must be digitized or drawn on the planning CT scan DRRs or on standard orthogonal x-ray films.

6.4.2 To ensure quality assurance, a planning CT scan with a scout film indexed through the cuts along with simulation films must be submitted.

6.5 Critical Structures

6.5.1 Dose limits: Every effort must be made to minimize the normal tissue volume treated.
- Liver: 60% must be below 30 Gy and 33% must be below 20 Gy.
- Kidneys: 75% of an entire kidney must be below 18 Gy.
- Spinal Cord: The maximum dose is 45 Gy.

6.6 Quality Assurance Documentation

6.6.1 Within 7 days after the start of treatment, the following data should be forwarded to RTOG Headquarters (Attn: Dosimetry)

6.6.1.1 CT scan and/or MRI showing the extent of the tumor with contrast; simulation films or DRRs designating the treatment field and GTV (including lymph nodes considered to contain tumor), liver, spinal cord, and kidneys, for AP and lateral fields; the RT prescription; the RT calculations and portal films corresponding to the simulation films or DRRs; a copy of the daily calculations; and any relevant beam data associated with any modification of treatment submission. (10/20/05)

6.6.1.2 A copy of the daily treatment record, isodose distribution on a transverse plane containing the central axis indicating the positions of the spinal cord, liver, and kidneys, color DVHs if the treatment planning system provides this output must be submitted to RTOG Headquarters within 1 week of RT end. (9/8/05)

6.7 Compliance Criteria

The following criteria will be used to evaluate RT compliance:

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Total Dose</th>
<th>Elapsed Days</th>
<th>Cord Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Protocol</td>
<td>≤ 5%</td>
<td>37-43</td>
<td>≤ 45 Gy</td>
</tr>
<tr>
<td>Variation Acceptable</td>
<td>&gt; 5%≤10%</td>
<td>44-50</td>
<td>&gt; 45 ≤ 47 Gy</td>
</tr>
<tr>
<td>Deviation Unacceptable</td>
<td>&gt;10%</td>
<td>&gt; 50</td>
<td>&gt; 47 Gy</td>
</tr>
</tbody>
</table>

6.8 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chairs, Christopher Crane, MD and William F. Regine, MD, will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. They will continue to review the data on a consistent basis. All cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters. These reviews will be on-going and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

6.9 Radiation Adverse Events

6.9.1 See Section 7.4.1 for dose modifications for RT and drug.

6.10 Radiation Adverse Event Reporting

Refer to Section 7.7 for Adverse Event Reporting

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Note: All patients must be on a proton pump inhibitor (lansoprazole, omeprazole, pantoprazole sodium, rabeprazole sodium). If any new epigastric pain develops, ulceration should be expected and sucralfate should be started. Upper endoscopy should be performed as clinically directed.
7.1 Capecitabine (Xeloda®) (7/29/05)

See package insert for further information.

7.1.1 Overview: Capecitabine is an oral prodrug of 5-fluorouracil. Metabolized in the liver to 5'-deoxyfluorocytidine, subsequently converted to 5'-deoxy-5-fluorouridine, which is then hydrolyzed to 5-fluorouracil (active). Peak plasma levels occur in 90 minutes, and elimination half-life is 45 minutes.

7.1.2 Formulation: Capecitabine is supplied as a biconvex, oblong film-coated tablet for oral administration in 500 mg tablets.

7.1.3 Storage and stability: Tablets should be stored at controlled room temperature (25°C) in tightly closed containers with excursions to 15°C to 30°C permitted.

7.1.4 Administration: Food delays the time to peak plasma level by about 90 minutes, and reduces the peak plasma concentration about 60%. Despite the effects of food on capecitabine pharmacokinetics, the manufacturer recommends giving the drug at the end of a meal because established safety and efficacy data are based on administration with food. The capecitabine daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal, and the tablets should be taken with water. See Appendix VI for the capecitabine dosing table. Patients will be asked to maintain a pill diary documenting self-administration of capecitabine (Appendix V).

7.1.5 Adverse Events: Common side effects from capecitabine include diarrhea (which may be severe), dermatologic effects (hand-and-foot syndrome referred to as palmar-plantar erythodyssesthesia) hematologic effects (neutropenia, thrombocytopenia, anemia and lymphopenia), weight gain, gastrointestinal effects (diarrhea, nausea, vomiting stomatitis, abdominal pain and constipation. Uncommon side effects include hepatotoxicity (hyperbilirubinemia). Rare side effects may include cardiovascular effects (myocardial infarction, dysrhythmias, cardiomyopathy).

7.1.6 Drug Interactions:

7.1.6.1 Antacids: The administration of 20 mL of an antacid containing aluminum hydroxide and magnesium hydroxide may result in an increase in the area under the concentration-time curve (AUC) and maximum concentration (Cmax) of capecitabine of 16% and 35%, respectively. These changes were not considered clinically significant.

7.1.6.2 Oral Anticoagulants: Altered coagulation parameters and/or bleeding, including death, have been reported in patients receiving capecitabine and coumadin-derivative anticoagulants. Post-marketing reports have revealed clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants when capecitabine was initiated. These events occurred within several days to several months after concurrent therapy was initiated. Patients receiving capecitabine and an oral anticoagulant should be closely and regularly monitored.

7.1.6.3 Phenytoin: Some patients receiving capecitabine and phenytoin may experience phenytoin toxicity as a result of increased phenytoin plasma levels. Phenytoin levels should be closely monitored in patients taking concomitant phenytoin and capecitabine. The dose of phenytoin may need to be reduced.

7.1.7 Supply: Capecitabine (Xeloda®): is commercially available. (7/29/05)(11/17/05)

7.1.8 Schedule: See tables in Section 7.4.

7.2 Gemcitabine HCl

See package insert for further information.

7.2.1 Overview: Gemcitabine is an antineoplastic agent that is structurally related to cytarabine. It is a pyrimidine analogue that is cell-cycle specific. Gemcitabine is cytotoxic to cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is converted intracellularly to gemcitabine-5'-triphosphate, its active form. Steady-state plasma levels of gemcitabine occur within 15 minutes after starting the infusion. The elimination half-life of gemcitabine ranges from 32 to 638 minutes, depending on the age and gender of the patient and the rate of administration of gemcitabine.

7.2.2 Formulation: Gemcitabine is available commercially as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloric salt (expressed as the free base) formulated with mannitol and sodium acetate.

7.2.3 Preparation: Drug vials will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL. The concentration for 200 mg and 1g vials should be no greater than 40 mg/mL.
7.2.4 Administration: An appropriate amount of drug will be prepared with normal saline and administered as a 30-minute intravenous infusion.

7.2.5 Storage and Stability: The lyophilized product should be stored at controlled room temperature (20° to 25° C) (68° to 79° F). Once the drug has been reconstituted it should be stored at controlled room temperature and used within 24 hours. The manufacturer recommends not to refrigerate solutions of gemcitabine as crystallization may occur.

7.2.6 Adverse Events: The major side effects observed with gemcitabine include leukopenia, thrombocytopenia, anemia, and a collection of signs and symptoms referred to collectively as a flu-like syndrome with fever, headache, rigors, nausea, diarrhea, itchy skin rash, myalgia, and anorexia. Other side effects have included fatigue, peripheral edema, and proteinuria. Less likely side effects include abnormal renal and liver function tests, vomiting, constipation, malaise, and anorexia. Rare side effects include Stevens-Johnson syndrome (severe skin reaction) and shortness of breath, cough, inflammation or scarring of the lung. Rare side effects have included hemolytic uremic syndrome/renal failure and liver failure, which have occurred following therapeutic gemcitabine therapy. Cardiac dysfunction (myocardial infarction, congestive heart failure, and atrial fibrillation) have been infrequently reported.

7.2.7 Supply: Gemcitabine is commercially available.

7.2.8 Schedule: See tables in Section 7.4.

7.3 Bevacizumab (rhuMAb VEGF, NSC 704865) (3/8/05)

7.3.1 Classification: Recombinant humanized monoclonal antibody

7.3.2 Molecular Weight: Approximate molecular weight is 149,000 Daltons

7.3.3 Mode of Action: Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors, resulting in inhibition of angiogenesis.

7.3.4 Description: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of a human IgG framework and murine antigen-binding complementarity-determining regions.

7.3.5 Formulation: Bevacizumab is manufactured by Genentech as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 5-cc (100-mg, 25-mg/mL) glass vial contains sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. The vials contain no preservative and are for single use only. It is CTEP’s routine policy that all investigational drugs supplied by the CTEP Pharmaceutical Management Branch for clinical trial use be specifically labeled on each container. For bevacizumab, the label reads “Caution: NEW DRUG – Limited by Federal (U.S.A.) law to investigational use”. The investigational bevacizumab is to be identified and handled as any investigational product. The product must be used only for patients enrolled in the clinical study.

The bevacizumab to be supplied for this protocol is intended for clinical trial use only and is not the commercially available Avastin. Investigational bevacizumab and commercially available Avastin may be produced at separate facilities and some difference may exist between the two products, although both are required to meet similar product testing criteria and are expected to be very similar in safety and activity. For further details and molecule characterization, see the updated bevacizumab Investigator Brochure.

7.3.6 Preparation: Vials contain no preservatives and are intended for single use only. The calculated dose of bevacizumab should be placed in a sterile, empty IV bag and diluted with a sufficient amount of 0.9% sodium chloride for injection to obtain a final volume of 100 mL.

7.3.7 Administration: Administration will be as a continuous IV infusion. Bevacizumab administration should follow chemotherapy administration if applicable.

The initial bevacizumab 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 a bevacizumab infusion–associated adverse event (mild fever and chills), he or she may be premedicated with Tylenol and Benadryl for the next bevacizumab infusion; however, the infusion time for all subsequent infusions should be the shortest period that was well tolerated. 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 30-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.
To ensure complete delivery of bevacizumab, the infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

1. When the bevacizumab infusion is complete, add an additional 50 mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.

2. Replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.

Please note: The flush is not included in the total recommended infusion times.

### Storage and Stability

7.3.8 Storage and stability: Upon receipt of the bevacizumab, vials are to be refrigerated at 2° to 8°C (36° to 46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. 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. Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single-use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry. Once bevacizumab has been added to a bag of sterile saline, the solution must be administered within 8 hours.

### Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (NSC 704865) (4/21/06)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold and italicized** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.cancer.gov/reporting/adeers.html](http://ctep.cancer.gov/reporting/adeers.html) for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Bevacizumab.

**Version 1.1, March 28, 2006**

<table>
<thead>
<tr>
<th>Category (Body System)</th>
<th>Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)</th>
<th>'Agent Specific Adverse Event List' (ASAEL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Allergic reaction/hypersensitivity (including drug fever)</td>
<td>Allergic reaction/hypersensitivity (including drug fever)</td>
</tr>
<tr>
<td></td>
<td>Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)</td>
<td></td>
</tr>
<tr>
<td>BLOOD/BONE MARROW</td>
<td>Leukocytes (total WBC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td></td>
</tr>
<tr>
<td>CARDIAC ARRHYTHMIA</td>
<td>Supraventricular arrhythmia NOS</td>
<td></td>
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<tr>
<td></td>
<td>Ventricular fibrillation</td>
<td></td>
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<tr>
<td>CARDIAC GENERAL</td>
<td>Cardiac ischemia/infarction</td>
<td>Cardiac ischemia/infarction</td>
</tr>
<tr>
<td></td>
<td>Cardiac troponin I (cTnI)</td>
<td></td>
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<tr>
<td></td>
<td>Hypertension</td>
<td>Hypertension</td>
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<tr>
<td></td>
<td>Hypotension</td>
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<tr>
<td></td>
<td>Left ventricular diastolic dysfunction</td>
<td></td>
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<tr>
<td></td>
<td>Left ventricular systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>CONSTITUTIONAL SYMPTOMS</td>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever (in the absence of neutropenia, where neutropenia is defined as ANC &lt;1.0 x 10⁹/L)</td>
<td>Fever (in the absence of neutropenia, where neutropenia is defined as ANC &lt;1.0 x 10⁹/L)</td>
</tr>
<tr>
<td></td>
<td>Rigors/chills</td>
<td>Rigors/chills</td>
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<tr>
<td><strong>DERMATOLOGY/SKIN</strong></td>
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<td></td>
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<tr>
<td>Pruritus/itching</td>
<td></td>
<td></td>
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<tr>
<td>Rash/desquamation</td>
<td>Rash/desquamation</td>
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<tr>
<td>Ulceration</td>
<td></td>
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<tr>
<td>Urticaria (hives, welts, wheals)</td>
<td>Urticaria (hives, welts, wheals)</td>
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<tr>
<td>Wound complication, non-infectious</td>
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<table>
<thead>
<tr>
<th><strong>GASTROINTESTINAL</strong></th>
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</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Colitis</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Constipation</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Fistula, GI - Select</td>
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</tr>
<tr>
<td>Heartburn/dyspepsia</td>
<td>Heartburn/dyspepsia</td>
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<tr>
<td>Leak (including anastomotic), GI: large bowel</td>
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</tr>
<tr>
<td>Mucositis/stomatitis (functional/symptomatic) - Select</td>
<td>Mucositis/stomatitis (functional/symptomatic) - Select</td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea</td>
</tr>
<tr>
<td>Perforation, GI - Select</td>
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<tr>
<td>Vomiting</td>
<td>Vomiting</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>HEMORRHAGE/BLEEDING</strong></th>
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</thead>
<tbody>
<tr>
<td>Hemorrhage GI - Select</td>
<td>Hemorrhage GI - Select</td>
</tr>
<tr>
<td>Hemorrhage, CNS</td>
<td>Hemorrhage, CNS</td>
</tr>
<tr>
<td>Hemorrhage, GU: vagina</td>
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</tr>
<tr>
<td>Hemorrhage, pulmonary/upper respiratory: lung</td>
<td>Hemorrhage, pulmonary/upper respiratory: lung</td>
</tr>
<tr>
<td>Hemorrhage, pulmonary/upper respiratory: nose</td>
<td>Hemorrhage, pulmonary/upper respiratory: nose</td>
</tr>
<tr>
<td>Hemorrhage/Bleeding - Other (varices-gastric/esophagus)</td>
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<tr>
<th><strong>INFECTION</strong></th>
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</thead>
<tbody>
<tr>
<td>Infection with normal ANC or Grade 1 or 2 neutrophils - Select</td>
<td>Infection with normal ANC or Grade 1 or 2 neutrophils - Select</td>
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<table>
<thead>
<tr>
<th><strong>METABOLIC/LABORATORY</strong></th>
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</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
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</tr>
<tr>
<td>ALT, SGPT (serum glutamic pyruvic transaminase)</td>
<td></td>
</tr>
<tr>
<td>AST, SGOT (serum glutamic oxaloacetic transaminase)</td>
<td></td>
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<tr>
<td>Bilirubin (hyperbilirubinemia)</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
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<tr>
<td>Proteinuria</td>
<td>Proteinuria</td>
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<table>
<thead>
<tr>
<th><strong>NEUROLOGY</strong></th>
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<tbody>
<tr>
<td>CNS cerebrovascular ischemia</td>
<td>CNS cerebrovascular ischemia</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Neurology – Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome (RPLS))</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>PAIN</strong></th>
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<tbody>
<tr>
<td>Pain - abdomen NOS</td>
<td></td>
</tr>
<tr>
<td>Pain - chest/thorax NOS</td>
<td>Pain - chest/thorax NOS</td>
</tr>
<tr>
<td>Pain - head/headache</td>
<td>Pain - head/headache</td>
</tr>
<tr>
<td>Pain - joint</td>
<td>Pain - joint</td>
</tr>
<tr>
<td>Pain - muscle</td>
<td></td>
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<tr>
<td>Pain - NOS</td>
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</tr>
<tr>
<td><strong>PULMONARY/UPPER RESPIRATORY</strong></td>
<td></td>
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<tr>
<td>-------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Bronchospasm, wheezing</td>
<td>Cough</td>
</tr>
<tr>
<td>Cough</td>
<td>Cough</td>
</tr>
<tr>
<td>Dyspnea (shortness of breath)</td>
<td></td>
</tr>
<tr>
<td>Nasal cavity/paranasal sinus reactions</td>
<td>Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)</td>
</tr>
<tr>
<td>Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)</td>
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<table>
<thead>
<tr>
<th><strong>RENAL/GENITOURINARY</strong></th>
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<tbody>
<tr>
<td>Renal/Genitourinary - Other (nephrotic syndrome)</td>
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<table>
<thead>
<tr>
<th><strong>SYNDROMES</strong></th>
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</thead>
<tbody>
<tr>
<td>Cytokine release syndrome/acute infusion reaction</td>
<td>Cytokine release syndrome/acute infusion reaction</td>
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<table>
<thead>
<tr>
<th><strong>VASCULAR</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis/thrombus/embolism</td>
<td>Thrombosis/thrombus/embolism</td>
</tr>
<tr>
<td>Visceral arterial ischemia (non-myocardial)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Bevacizumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

1. This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting ADEERSMD@techres.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on Bevacizumab trials but with the relationship to Bevacizumab still undetermined:

**BLOOD/BONE MARROW** - Hemoglobin; idiopathic thrombocytopenia purpura; platelets

**CARDIAC GENERAL** - Cardiac arrest; pericardial effusion

**COAGULATION** - DIC

**DEATH** - Sudden death (cause unknown)

**DERMATOLOGY/SKIN** - Hypopigmentation

**GASTROINTESTINAL** - Rectal abscess/necrosis; small bowel obstruction; taste alteration

**METABOLIC/LABORATORY** - Hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia

**MUSCULOSKELETAL/SOFT TISSUE** - Aseptic necrotic bone; gait/walking; myasthenia gravis

**NEUROLOGY** - Aseptic meningitis; confusion; encephalopathy; peripheral neuropathy; seizure; syncope

**OCULAR/VISUAL** - Cataract; watery eye

**PULMONARY/UPPER RESPIRATORY** - ARDS; pneumonitis/pulmonary infiltrates; pneumothorax

**RENAL/GENITOURINARY** - Urinary frequency

Note: Bevacizumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3.10 Accountability and Supply (3/8/05)
The Principal Investigator (or authorized designee listed by the Investigator on the site’s most recent Supplemental Investigator Data Form [IDF] on file with the PMB) at each participating institution may request bevacizumab from NCI’s Pharmaceutical Management Branch (PMB). The updated version (11/10/03) of each institution’s Drug Authorization Review and Tracking System (DARTS) will require selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the Investigator during the annual Investigator registration process. This process must be completed before a drug order can be entered for that investigator. Any changes to this information will require updating the first two pages of the IDF, having the Investigator sign the revised IDF, and returning it to the PMB via fax at 301-402-4870. Questions about the process should be directed to the PMB at 301-496-5725 Monday through Friday from 8:30 – 4:30 Eastern Time. PMB policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions unless prior approval from PMB is obtained. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN, Room 7149, Bethesda, MD 20892.] All forms can be accessed on the NCI web site, [http://ctep.cancer.gov/forms/index.html](http://ctep.cancer.gov/forms/index.html)

Investigator’s Brochures may be obtained from PMB for investigational agents where CTEP holds the IND. To receive an Investigator’s Brochure, you must be an active participant on an NCI sponsored clinical trial and have an active investigator registration status. Contact the IB
Coordinator at IBCoordinator@mail.nih.gov <mailto:IBCoordinator@mail.nih.gov> or 301-496-5725, Monday through Friday, from 8:30 a.m. to 4:30 p.m. Eastern time.

7.3.11 Drug Inventory Records
The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCTD, using the NCI Drug Accountability Record Form (see the NCI Investigators Handbook for Procedures for Drug Accountability and Storage).

7.3.12 Schedule: See tables in Section 7.4.

7.4 Treatment (7/29/05) (10/20/05) (4/21/06)
Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS (reversible posterior leukoencephalopathy syndrome), pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.

Note: All patients must be on a proton pump inhibitor (lansoprazole, omeprazole, pantoprazole sodium, rabeprazole sodium). If any new epigastric pain develops, ulceration should be expected and sucralfate should be started. Upper endoscopy should be performed as clinically directed.

### Capecitabine and Bevacizumab with Concurrent Radiation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine (refer to Appendix VI) + Bevacizumab</td>
<td>825 mg/m² po</td>
<td>q 12 hours Monday through Friday on radiation days</td>
<td></td>
</tr>
<tr>
<td>5 mg/kg IV</td>
<td></td>
<td>On days 1, 15, and 29 of chemoradiation.</td>
<td></td>
</tr>
</tbody>
</table>

#### Anticoagulant guidelines during concurrent chemotherapy/RT

<table>
<thead>
<tr>
<th>Chemotherapy Agent</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>capcitabine</td>
<td>bevacizumab</td>
</tr>
<tr>
<td>Prophylactic low molecular weight heparin</td>
<td>Continue</td>
</tr>
<tr>
<td>Therapeutic heparin</td>
<td>Stop</td>
</tr>
<tr>
<td>warfarin</td>
<td>Stop</td>
</tr>
</tbody>
</table>

#### CT Evaluation for Progression 3-4 Weeks After the End of Concurrent Radiation

#### Maintenance Gemcitabine and Bevacizumab
Maintenance gemcitabine and bevacizumab must start no sooner than 4 weeks after completion of chemoradiation and no later than 7 weeks after completion of chemoradiation. Hematologic parameters of ANC ≥ 1,500 mm³ and platelets ≥ 100,000 µl must be met before the start of therapy.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine + Bevacizumab</td>
<td>1,000 mg/m² IV</td>
<td>Weekly for 3 weeks, then 1 week off, continuing until progression</td>
<td></td>
</tr>
<tr>
<td>5 mg/kg IV</td>
<td></td>
<td>Bevacizumab maintenance will begin with the first dose of gemcitabine then continue every 2 weeks, continuing until progression</td>
<td></td>
</tr>
</tbody>
</table>

#### Anticoagulant guidelines during maintenance therapy

<table>
<thead>
<tr>
<th>Chemotherapy Agent</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>gemcitabine</td>
<td>bevacizumab</td>
</tr>
<tr>
<td>Prophylactic heparin</td>
<td>Continue</td>
</tr>
<tr>
<td>Therapeutic heparin</td>
<td>Continue</td>
</tr>
<tr>
<td>warfarin</td>
<td>Continue</td>
</tr>
</tbody>
</table>
7.4.1 Dose Modifications:

7.4.1.1 Dose Modifications for Bevacizumab (for both concurrent and maintenance therapy): (10/20/05)

There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below:

7.4.1.1.1 Hemorrhage (7/29/05)
- Grade 3 or 4: Any patient who experiences grade 3 or 4 bleeding will be removed from protocol treatment.

7.4.1.1.2 Arterial thrombosis (7/29/05)
(Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, or any other arterial thromboembolic events)
- ≥ Grade 2: discontinue bevacizumab

7.4.1.1.3 Venous Thrombosis (7/29/05)
- Grade 3: Hold bevacizumab treatment. If full-dose anticoagulant is needed during concurrent chemoradiation, hold bevacizumab for two weeks following the last full-dose anticoagulant period.
- Grade 4: discontinue bevacizumab

7.4.1.1.4 Coagulation: For patients on therapeutic anticoagulation, PT INR or PTT (whichever appropriate) should be monitored closely during bevacizumab therapy. Bevacizumab should be held if the coagulation parameters are higher than the intended therapeutic range.

7.4.1.1.5 Hypertension
- Hypertension should be treated with anti-hypertensive medication as per general practice.
- For controlled hypertension: continue therapy.
- For persistent or symptomatic hypertension: hold bevacizumab therapy.
  If treatment is delayed for > 4 weeks due to uncontrolled hypertension, patients should be removed from protocol treatment.
- Grade 4: The patient should be removed from protocol treatment.

7.4.1.1.6 Proteinuria: Proteinuria of > 2+ (as determined by urine dipstick) or UPC ratio of > 1.5 requires holding bevacizumab treatment and performing a 24-hour urine collection to determine total protein.
- If proteinuria is < 2000 mg/24 hours, continue bevacizumab.
- If proteinuria is > 2000 mg/24 hours, hold bevacizumab until urine protein recovered to < 2000 mg/24hr.
- If nephrotic syndrome (G4) occurs, discontinue bevacizumab.

7.4.1.1.7 Wound dehiscence requiring medical or surgical intervention: discontinue bevacizumab.

7.4.1.1.8 Bowel perforation or tumor ulceration into the stomach or small bowel. In the event of bowel perforation discontinue bevacizumab. Furthermore, any patient who develops tumor invasion into the mucosa of the stomach or small bowel or has ulceration of the stomach or small bowel from tumor may be at increased risk for perforation, fistula or bleeding and will be removed from protocol treatment.

7.4.1.1.9 Other grade 3 or 4 non-hematological adverse events (except fatigue or cholangitis): (7/29/05) If a patient develops any grade 3 or 4 non-hematological adverse events, bevacizumab should be held until symptoms resolve to ≤ grade 1. If a grade 3 or 4 adverse event persists for > 3-4 weeks or recurs after resumption of the therapy, the patient will be removed from protocol treatment.

7.4.1.1.10 Hematologic: For grade 3 or 4 thrombocytopenia (platelets < 50,000/ul), hold bevacizumab until platelets > 50,000/ul.
### RT/CHEMOTHERAPY MODIFICATION

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Parameters</th>
<th>Agent</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>ANC &gt;1000 &amp; platelets &gt; 75,000</td>
<td>Capecitabine</td>
<td>Full dose</td>
</tr>
<tr>
<td></td>
<td>ANC 500-999 &amp;/or platelets 50,000-75,000</td>
<td>Capecitabine</td>
<td>Hold until ANC &gt; 1000 and platelets &gt; 75,000; resume at 25% dose reduction</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 500 &amp;/or platelets &lt; 50,000</td>
<td>Capecitabine Radiation</td>
<td>Hold radiation and capecitabine until ANC &gt;1000 and platelets &gt;75,000; resume capecitabine at 25% dose reduction</td>
</tr>
</tbody>
</table>

**Note:** Patients who have required two dose reductions and experience a third episode of ANC < 1000 or platelets < 75,000, will complete RT and bevacizumab but will not receive any more capecitabine.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Parameters</th>
<th>Agent</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea (all stools/day &gt; pretreatment)</td>
<td>Grade 1 (2-3 stools/day)</td>
<td>Capecitabine</td>
<td>Maintain dose</td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; occurrence Grade 2 (4-6 stools/day)</td>
<td>Capecitabine</td>
<td>Hold until Grade 0-1; resume at 25% dose reduction</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; &amp; 3&lt;sup&gt;rd&lt;/sup&gt; occurrence of grade 2</td>
<td>Capecitabine</td>
<td>Hold until Grade 0-1; resume @ 50% dose reduction</td>
</tr>
<tr>
<td></td>
<td>Grade 3 (7 or more stools over baseline or IVF &gt;24hr; hospitalization needed)</td>
<td>Radiation</td>
<td>Hold until resolves to ≤ Grade 2</td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; occurrence Grade 3 (7-9 stools/day)</td>
<td>Capecitabine</td>
<td>Hold until Grade 0-1; resume with 25% dose reduction</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; &amp; 3&lt;sup&gt;rd&lt;/sup&gt; occurrence Grade 3 (7-9 stools/day)</td>
<td>Capecitabine</td>
<td>Hold until Grade 0-1; resume with 50% dose reduction</td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Occurrence Grade 3 (≥10 stools/day)</td>
<td>Capecitabine</td>
<td>Hold until Grade 0-1; resume at 50% dose reduction</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Occurrence Grade 3 (≥10 stools/day)</td>
<td>Capecitabine</td>
<td>Hold until Grade 0-1; resume at 50% dose reduction</td>
</tr>
<tr>
<td>Hand/foot syndrome</td>
<td>Grade 2</td>
<td>Capecitabine</td>
<td>Hold until it resolves to ≤ Grade 1; resume at 25% dose reduction</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Capecitabine</td>
<td>Hold until it resolves to ≤ Grade 1; resume at 50% dose reduction</td>
</tr>
<tr>
<td>Other nonhematologic toxicities (except fatigue or cholangitis)</td>
<td>Grade 3 or 4 1&lt;sup&gt;st&lt;/sup&gt; episode</td>
<td>Capecitabine</td>
<td>Hold until it resolves to ≤ Grade 2; resume at 25% dose reduction (dose reduction is permanent)</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; episode</td>
<td>Capecitabine</td>
<td>Hold until it resolves to ≤ Grade 2; resume with another 25% dose reduction (dose reduction is permanent)</td>
</tr>
<tr>
<td></td>
<td>≥ Grade 3</td>
<td>Radiation</td>
<td>Hold until it resolves to ≤ Grade 2</td>
</tr>
</tbody>
</table>
### 7.4.1.3 Dose Modifications for Gemcitabine (7/29/05)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Parameters</th>
<th>Agent</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td>ANC 1000-1499 or platelets 75,000-99,000</td>
<td>Gemcitabine</td>
<td>25% dose reduction</td>
</tr>
<tr>
<td></td>
<td>ANC &lt;1,000 or platelet &lt;75,000</td>
<td>Gemcitabine</td>
<td>Hold Repeat blood work in one week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Restart when ANC ≥ 1,000 and Platelets ≥ 75,000</td>
</tr>
<tr>
<td></td>
<td>ANC &lt;500 or platelets &lt;50,000</td>
<td>Gemcitabine</td>
<td>Hold; resume when ANC &gt;1000 and platelets &gt;75,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>at a 25% dose reduction (permanent)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; episode of grade 4 neutropenia or grade 3 thrombocytopenia</td>
<td>Gemcitabine</td>
<td>Hold; resume when ANC &gt;1000 and platelets &gt;75,000 at another 25% dose reduction</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Episode</td>
<td>Gemcitabine</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4 nonhematologic adverse events other than fatigue or cholangitis</td>
<td>Gemcitabine</td>
<td>Hold until resolved to ≤ Grade 2; 25% dose reduction (permanent)</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Occurrence</td>
<td>Gemcitabine</td>
<td>Hold until resolved to ≤ Grade 2; another 25% reduction</td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Occurrence</td>
<td>Gemcitabine</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Occurrence</td>
<td>Gemcitabine</td>
<td>Discontinue</td>
<td></td>
</tr>
</tbody>
</table>

#### 7.5 Criteria for Removal From Protocol Treatment (7/29/05)
- Progression of disease
- **Adverse events as specified in Section 7.4.1 as well as for life-threatening cardiac arrhythmia or life-threatening congestive heart failure** – reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and RTOG Headquarters’ Data Management must be notified
- The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters’ Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual.
- An arterial thromboembolic event of any grade

#### 7.6 Modality Review
The Medical Oncology Co-Chair, Howard Safran, MD will perform a Medical Oncology Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: per protocol; variation, acceptable; deviation unacceptable; not evaluable for chemotherapy review, or, incomplete chemotherapy. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Reviews will begin after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. The medical oncologist co-chair will continue to review the data on a consistent basis. All cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters.

#### 7.7 Adverse Events (7/29/05)
This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The CTEP home page also can be accessed from the
All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

7.7.1 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762 (available 24 hours/day)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient’s case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1). NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.

7.7.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported to RTOG (SAE PHONE: 215-717-2762, available 24 hours/day) within 24 hours of discovery of the event.

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller’s contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS within 5 or 10 calendar days of the initial phone report, as directed by the Data Manager taking the call. SAEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.
SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.7.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at [http://ctep.cancer.gov/forms/index.html](http://ctep.cancer.gov/forms/index.html). The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>

7.8 AdEERS Expedited Reporting Requirements

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Investigational Agent bevacizumab in this Study

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5</th>
<th>Grades 4 &amp; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected with Hospitalization</td>
<td>Expected without Hospitalization</td>
<td>Expected with Hospitalization</td>
<td>Expected without Hospitalization</td>
</tr>
<tr>
<td>Unexpected</td>
<td>Expected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexpected with Hospitalization</td>
<td>Expected without Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>24-Hour; 5 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
</tbody>
</table>

1 Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
- AdEERS 10 calendar day report:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 5 expected events

2 Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” – A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
• Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
• Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
• Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

An investigational agent supplied under a CTEP-IND is being used in combination with commercial agents. The combination should be considered investigational, and reporting should follow the guidelines described above.

7.9 Clinical Trials Agreement (3/8/05) (7/29/05)

The agent(s) bevacizumab (rhuMAb VEGF;) supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Genentech, Inc. Pharmaceutical Company (ies) (hereinafter referred to as “Collaborator(s)” and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as “Multi-Party Data”:

   a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI’s participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

   When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator’s wish to contact them.

4. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: anshers@ctep.nci.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

8.0 SURGERY
In patients with a marked response to treatment, surgery may be attempted based on the discretion of the attending surgeon. Chemotherapy, radiation, and bevacizumab should be stopped at least 4 weeks prior to attempted surgery and not restarted until at least 4 weeks after surgery and after the wound is fully healed. If there are wound healing complications, or if treatment has to be delayed for > 8 weeks after surgery for any reasons, the patient should be removed from the protocol therapy.

9.0 OTHER THERAPY
9.1 Ancillary Therapy (10/20/05):
Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the appropriate forms and in your source documentation. Erythropoietin is allowed. Myeloid growth factors (e.g., Neupogen, Neulasta) should not be used prophylactically but may be utilized to treat Grade 3/4 ANC.

9.2.1 Required Concomitant Medications
All patients must be on a proton pump inhibitor (lansoprazole, omeprazole, pantoprazole sodium, rabeprazole sodium). If any new epigastric pain develops, ulceration should be expected and sucralfate should be started. Upper endoscopy should be performed as clinically directed.

9.2.2 Prohibited Concomitant Medications (7/29/05) (10/20/05)
Patients may receive all concomitant therapy deemed necessary to provide adequate support, with the exception of the therapies detailed below:
- other investigational agents
- other cytotoxic agents or radiotherapy
- sorivudine or brivudine A
- cimetidine
- warfarin sodium (during concurrent chemotherapy/RT)
- Therapeutic heparin (during concurrent chemotherapy/RT)
- Neumega

10.0 TISSUE/SPECIMEN SUBMISSION
10.1 Tissue/Specimen Submission
The RTOG Tissue Bank at LDS Hospital in Utah acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Tissue Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Tissue Bank also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the RTOG tissue bank for the purpose of tissue banking.
10.2 Specimen Collection for Tissue Banking

The following must be provided in order for the case to be evaluable for the Tissue Bank:

10.2.1 One H&E stained slide
10.2.2 A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.3 A Pathology Report documenting that the submitted block, core, or slides contain tumor. The report must include the RTOG protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Tissue Bank. The form must include the RTOG protocol number and patient’s case number.

10.2.5 Submit materials for Tissue Banking to:

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
holly.goold@ihc.com

10.4 Reimbursement

RTOG will reimburse submitting institutions $200 per case for a block or core of material, or $100 per case for unstained slides. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.5 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/tissuebank/tissuefaq.html for further details.)

10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The RTOG Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.
11.0  PATIENT ASSESSMENTS

11.1  Study Parameters  (7/29/05) (10/20/05)

<table>
<thead>
<tr>
<th></th>
<th>Within 14 days prior to study entry</th>
<th>Weekly Chemo-</th>
<th>Chemo-radiation Completion</th>
<th>During Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance Status</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>Physical Examination:</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X</td>
<td>Every 2 weeks</td>
<td>Weekly</td>
</tr>
<tr>
<td>Adverse event</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Diff, Platelets</td>
<td>X</td>
<td>X</td>
<td>X c</td>
<td>Weekly b</td>
</tr>
<tr>
<td>Glucose, Electrolytes</td>
<td>X</td>
<td>X</td>
<td>X c</td>
<td>Monthly</td>
</tr>
<tr>
<td>BUN, Calculated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine Clearance,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH, AST, ALT, Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, Coagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>panel, TP, Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA for proteinuria</td>
<td>X</td>
<td>X c</td>
<td>q 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X a</td>
<td></td>
<td>q 2 mos.</td>
<td></td>
</tr>
<tr>
<td>Abdominal CT/MRI</td>
<td>X a</td>
<td></td>
<td>X c</td>
<td>q 2 mos.</td>
</tr>
<tr>
<td>INR</td>
<td>X</td>
<td></td>
<td>X c</td>
<td></td>
</tr>
<tr>
<td>Blood Pregnancy Test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA 19-9</td>
<td>X a</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Radiologic studies must be done within 4 weeks of study entry  
b. Not required during week off of gemcitabine  
c. Must be done 3-4 weeks following chemoradiation completion  
d. Needs to be done within 7 days of study entry, for women of childbearing potential  
e. CA 19-9 to be drawn within 21 days of study entry  
f. With every F1 submission, per Section 12.

11.2  Response Assessment  

11.2.1  Measurement of Response

Response will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. **Note:** Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

**Measurable Disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (PET, CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

**Target Lesions:** All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

**Guidelines for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

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

**Conventional CT and MRI:** These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

### 11.2.2 Response Criteria—RECIST CRITERIA

Response and progression will be measured by comparing tumor size at time of study entry with measurements taken at every 2 months by CT/MRI. Confirmed Stable Disease (SD) or Partial Response (PR) on the repeat scans is required for assigning PR or SD as the best response.

#### 11.2.2.1 Evaluation of target lesions

- **Complete Response (CR):** Disappearance of all target lesions as measured by MRI, CT, or physical examination. This is the order of preference for measurement.
- **Partial Response (PR):** At least a 30% decrease in the sum of the longest diameter (LD) of target lesions. The order of preference for measurement is MRI, CT, or physical examination.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. The order of preference for measurement is MRI, CT, or physical examination.

#### 11.2.2.2 Evaluation of non-target lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level
- **Incomplete Response/ Stable Disease (SD):** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

**Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

### 11.2.2.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria (see Sections 11.2.2.1 and 11.2.2.4.1).

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Incomplete</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>response/SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

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

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

### 11.2.2.4 Confirmatory Measurement/Duration of Response

#### 11.2.2.4.1 Confirmation
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.2.2.3).

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

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

Data should be submitted to:

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (7/29/05)(9/8/05)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>RT Prescription <em>(Protocol Treatment Form)</em> (T2)</td>
<td>Within 1 wk of start of RT</td>
</tr>
<tr>
<td>Films <em>(simulation and portal)</em> for DRRs (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Treatment Planning CT/MRI Scan (C1)</td>
<td></td>
</tr>
<tr>
<td>Systemic Treatment During Radiotherapy Summary Form (TF)</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Adverse Event Form (AE) <em>(Report radiotherapy and chemotherapy related adverse events on the (AE) form submitted with the (TF) form.)</em></td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months x 2 years; every 6 months x 5 years; then annually. Also at progression/relapse and at death</td>
</tr>
<tr>
<td>Maintenance Chemotherapy Treatment Summary Form (SF)</td>
<td>Monthly, with the first being due 12 weeks post completion of RT</td>
</tr>
<tr>
<td>Adverse Event Form (AE) <em>(Report chemotherapy related Adverse Events on the AE form submitted with the (SF) form.)</em></td>
<td></td>
</tr>
<tr>
<td>Surgery Form (S1)</td>
<td>As applicable; see Section 8.0</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

12.2 Site Records

Site records must contain details regarding dosage, and start and stop dates of drug treatment. These records include documentation of tracking treatment compliance; ie, medical record notes, notations of telephone calls to the patient, patient diaries, etc.
This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.1 Study Endpoints

13.1.1 Primary Endpoint
- One-year overall survival rate (failure: death due to any cause).

13.1.2 Secondary Endpoints (7/29/05)
- Frequency of patients developing:
  - Unacceptable serious adverse events (defined per the CTCAE v. 3.0 as ≥ Grade 3 bowel perforation, ≥ Grade 3 or 4 bleeding, ≥ Grade 4 thrombotic event or ≥ Grade 3 arterial events (including vessel injury, visceral arterial ischemia, cardiac ischemia/infarction) attributable to protocol treatment.
  - Unacceptable adverse events (defined per the CTCAE v. 3.0 as ≥ Grade 3 GI bleeding occurring at any time or Grade 4 or higher nonhematologic adverse events occurring within 90 days of treatment start) attributable to protocol treatment.
  - Progression-free survival (failure: local, regional or distant progression or death due to any cause).
  - Response rate.

13.2 Sample Size

13.2.1 Sample Size Derivation
The primary objective of this study is to estimate the one-year overall survival rate. In the previous RTOG protocol for unresectable pancreatic cancer (RTOG 98-12), a one-year survival rate of approximately 43% was observed. There were 109 analyzable patients on RTOG 98-12 with 61 still at risk for death at one year. Using the method of Dixon and Simon, a sample size of 74 analyzable patients followed over 12 months will ensure at least 90% probability of detecting a minimum of 15% improvement in the one-year survival rate compared to RTOG 98-12 at the 0.10 significance level (with a one-sided test). Adjusting this figure by 10% to allow for patient ineligibility or loss, a total sample size of 82 patients will be required for this study.

13.2.2 Patient Accrual
Recent RTOG Phase II pancreas studies (98-12 & 00-20) accrued an average of 7.9 patients per month. Based upon this accrual rate, and allowing 6 months for institutional IRB review and approval, accrual should be completed in approximately 16 months. If the average monthly accrual is less than 2 cases per month, the study will be re-evaluated with respect to feasibility.

13.3 Suspension of Accrual Due to Excessive Adverse Events (AE) (7/29/05)

In the event that an early stopping rule is met, RTOG will notify both CTEP and the FDA.

13.3.1 Unacceptable Rate of Serious Adverse Events (7/29/05)
The rate of unacceptable serious adverse events (as defined in Section 13.1.2) will be evaluated at two time points during accrual, after 25 and 50 patients have been entered and are evaluable, and again on all evaluable patients after the study has finished accrual. The study chairs have determined that a rate of 15% or greater will be considered to be unacceptable. According to Flemming’s method with a maximum overall significance level of 0.05 if there are:

- 4 or more unacceptable serious adverse events out of the first 25 evaluable patients, or
- 5 or more unacceptable serious adverse events out of the first 50 evaluable patients,

the study will have exceeded the limit for unacceptable serious adverse events. The final analysis will use a rejection rule of 6 or more unacceptable serious adverse events out of 74 evaluable patients. If the number of unacceptable serious adverse events crosses a boundary, as described in the rules above, then the conclusion will be that the treatment-related unacceptable serious adverse event rate is greater than 15%. If this occurs, accrual will be suspended and the study chairs, RTOG Gastrointestinal Cancer Committee Chair, and the statistician will review the adverse event data and make appropriate recommendations to the RTOG Executive Committee about the study. These stopping rules provide 85% power for concluding that the unacceptable serious adverse event rate is equal to or exceeds 15% when in fact that is the true rate.

13.3.2 Unacceptable Rate of Adverse Events (7/29/05)
The rate of unacceptable adverse events (as defined in Section 13.1.2) will be evaluated at two time points during accrual, after 25 and 50 patients have been entered and are evaluable, and again on all evaluable patients after the study has finished accrual. The study chairs have
determined that a rate of 35% or greater will be considered to be unacceptable. According to Flemming’s method\textsuperscript{17} with a maximum overall significance level of 0.05 if there are:

- 10 or more unacceptable adverse events out of the first 25 evaluable patients, or
- 15 or more unacceptable adverse events out of the first 50 evaluable patients,

the study will have exceeded the limit for unacceptable adverse events. The final analysis will use a rejection rule of 19 or more unacceptable adverse events out of 74 evaluable patients. If the number of unacceptable adverse events crosses a boundary, as described in the rules above, then the conclusion will be that the treatment-related unacceptable adverse event rate is greater than 35%. If this occurs, the study chairs, RTOG Gastrointestinal Cancer Committee Chair, and the statistician will review the adverse event data and make appropriate recommendations to the RTOG Executive Committee about the study. These stopping rules provide 85% power for concluding that the unacceptable adverse event rate is equal to or exceeds 35% when in fact that is the true rate.

13.3.3 Fatal Treatment Morbidity

If there is any fatal treatment morbidity, the event will be reported to the study chairs and the RTOG Gastrointestinal Cancer Committee Chair for review.

13.4 Analysis Plan

13.4.1 Interim Reports

Interim reports will be prepared every six months until the primary endpoint has been presented. In general, these reports include:

- the patient accrual rate with projected completion date
- institutional accrual
- pretreatment characteristics
- compliance rates of treatment delivery with respect to the protocol prescription
- the frequency and severity of reported adverse events

13.4.2 Analysis for Reporting the Initial Treatment Results (7/29/05)

The major analysis for reporting the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are:

- tabulation of all cases entered, and any patients excluded from the analysis with reasons for exclusion
- institutional accrual
- patient accrual rate
- distribution of important prognostic baseline other pretreatment variables
- observed results with respect to the endpoints described in Section 13.1.

The estimated survival will be tested against the RTOG 98-12 trial with a one-sided log-rank test. Estimates of the median and one-year progression-free and overall survival rates will be estimated using the Kaplan-Meier method.

13.5 Inclusion of Women and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have considered differences in prognosis by race and gender. In an analysis of the RTOG pancreas database, we found no difference. No other study so far has indicated any significant racial or gender differences in treatment effects for unresectable pancreatic cancer patients. These issues are not well studied. The study was designed to test the efficacy under the assumption of the same efficacy across the genders and across the races. If the distributions allow, an exploratory statistical analysis will be performed to examine the possible difference between the genders and among the races.
## GENDER AND MINORITY ACCRUAL ESTIMATES

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<td><strong>47</strong></td>
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<td><strong>Racial Category: Total of all subjects</strong></td>
<td><strong>35</strong></td>
<td><strong>47</strong></td>
<td><strong>82</strong></td>
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</table>
REFERENCES


APPENDIX I

RTOG 0411

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE II STUDY OF BEVACIZUMAB WITH CONCURRENT CAPECITABINE AND RADIATION FOLLOWED BY MAINTENANCE GEMCITABINE AND BEVACIZUMAB FOR LOCALLY ADVANCED PANCREATIC CANCER

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have locally advanced pancreatic cancer. This means that you have a pancreatic cancer that cannot be removed by surgery but has not spread to other organs.

Why is this study being done? (3/8/05)

The purpose of this study is to find out what effects, good and bad, the anti-cancer drug bevacizumab has when added to chemotherapy and radiation for your type of pancreatic cancer.

Standard treatments for locally advanced pancreatic cancer involve the use of the chemotherapy drugs fluorouracil (capecitabine) and gemcitabine. This study adds bevacizumab to radiation, capecitabine and gemcitabine. Bevacizumab may block cancer cells from making new blood vessels. It also may help standard chemotherapy and radiation therapy to work better.

Bevacizumab has been approved by the FDA for use in colon cancer. The use of bevacizumab with chemotherapy and radiation in pancreatic cancer is experimental. Bevacizumab is the common name for the commercial drug Avastin. The bevacizumab used in this trial, however, is for use in research studies only and may be made at locations different from those where Avastin is made. Although some differences may exist, bevacizumab for research use and the commercial drug, Avastin, are manufactured by a similar process, meet similar standards for final product testing, and are expected to be very similar in safety and effectiveness.

How many people will take part in the study?

About 82 people will take part in this study.
What will happen if I take part in this research study?

If you agree to participate in this study, you will receive bevacizumab, capecitabine and radiation followed by bevacizumab and gemcitabine. The treatment will be given as follows:

Radiation Therapy: Radiation treatment to the abdomen will be given once a day, 5 days a week, for 5 and 1/2 weeks. Radiation treatments will take about 10 minutes. All radiation treatments will be given as an outpatient at your institution.

Chemotherapy: Starting the same day as your radiation treatments, you will receive capecitabine, which is a chemotherapy pill, twice a day, Monday through Friday, for 5 and 1/2 weeks, while you are receiving radiation therapy. The number of capecitabine pills you need to take each day is determined by your height and weight, but is usually between 4 to 8 pills per day. Three to four weeks after you have completed taking capecitabine and radiation you will be evaluated for growth of your cancer. If the cancer has not progressed, then 4-7 weeks after completing capecitabine and radiation, you will go on a maintenance treatment that includes gemcitabine. Gemcitabine will be given once a week for 3 weeks followed by one week off as long as your cancer does not grow and you do not have severe side effects. Gemcitabine is injected into a vein (intravenously) for about 30 minutes. Your gemcitabine treatments will be given as an outpatient at your institution.

Bevacizumab: Starting the same day as your first radiation treatment and capecitabine, you will receive bevacizumab by vein over 90 minutes as an outpatient at your institution. You will receive your second and third treatments with bevacizumab 2 and 4 weeks later by vein over 30-60 minutes. If your cancer has not grown during the period that you received capecitabine, bevacizumab, and radiation, then you will receive maintenance treatment that includes bevacizumab with gemcitabine. The bevacizumab will be given by vein every 2 weeks for about 30 minutes and continued as long as your cancer does not grow and you do not have severe side effects.

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical Exam
- Blood Tests
- Abdominal CT/MRI Scan
- Chest X-Ray

During the study … (3/8/05)
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Physical Exam  Weekly during radiation treatment, at the end of radiation treatment, and then monthly.
- Blood tests  Weekly.
- Abdominal CT/MRI  At the end of radiation treatment, then every two months.
- Chest X-ray  At the end of radiation treatment, then every two months.

How long will I be in the study?  (7/29/05)
Treatment with radiation, chemotherapy, and bevacizumab will last approximately five and a half weeks. You will continue with chemotherapy and bevacizumab indefinitely unless your cancer gets worse or you have side effects from the medication. You will have follow up exams indefinitely.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the chemotherapy and radiation. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.
Risks and side effects related to the radiation and chemotherapy include the following:

**Risks Associated with Radiation Therapy**

**Likely**
- Stomach pain and gastrointestinal discomfort, which usually occur during the last three weeks of radiation and generally go away within 2 months after the treatment is finished.
- Nausea
- Diarrhea
- Fatigue
- Tanning, redness of skin, and hair loss within the radiation area, which is temporary
- Skin in radiation treatment area may remain permanently dry
- Lower blood counts, which can cause fatigue and increase the risk of infection and bleeding
- Loss of appetite and weight loss

**Less Likely**
- Vomiting

**Rare But Serious**
- Change in liver or kidney function
- Bowel obstruction

**Risks Associated with Capecitabine**

**Likely**
- Nausea
- Diarrhea
- Mouth sores
- Weakness
- Fatigue
- Redness, drying of the skin especially the hands and feet.
- Skin or nail darkening
- Sores in the mouth
- Skin rash or peeling of skin on hands and feet
- Lower blood counts, which can cause fatigue and increase the risk of infection and bleeding
- Loss of appetite and weight loss

**Less Likely**
- Vomiting
- Muscle aches
- Constipation
- Hair loss

**Rare But Serious**
- Chest pain or irregular heartbeat
**Risks Associated with Gemcitabine**

*Likely*
- Low blood counts, which can cause fatigue and increase the risk of infection and bleeding
- Nausea
- Diarrhea
- Fatigue
- Fever
- Headache and chills
- Skin rash that may cause itching
- Loss of appetite

*Less Likely*
- Muscle aches
- Vomiting
- Constipation
- Change in liver function blood tests that may indicate problems with your liver. This would usually not give any symptoms but could cause jaundice (the skin to become yellow).

*Rare But Serious*
- Stevens-Johnson syndrome (severe skin reaction)
- Shortness of breath, cough, inflammation or scarring of the lung.

**Risks Associated with Bevacizumab (3/8/05) (4/21/06)**

*Likely*
- A mild allergic reaction with fever, chills, hives, and a rash while you receive bevacizumab, before the first chemotherapy/RT treatment
- High blood pressure
- Headache
- Loss of strength and energy
- Protein in the urine
- Weakness
- Dizziness

*Less Likely*
- Bleeding, which can be severe
- An allergic reaction with shortness of breath while you receive bevacizumab
- Nausea and vomiting
- A change in liver function tests which usually have no symptoms but could cause jaundice (the skin color turning yellow)
- Muscle, joint and chest pains
- Cough
- Voice change
Rare But Serious

- Perforation, which could be life threatening and fatal. This can cause a tear of the bowels and will cause pain and would need surgery to repair.
- Some patients who have participated in other studies of bevacizumab have developed blood clots in veins. Of a large number of patients treated for advanced colorectal cancer, 4 patients treated with bevacizumab died as a direct result of blood clots. Cancer patients (especially those with advanced disease) are known to be at high risk for blood clots. Compared to patients with advanced colorectal cancer who received chemotherapy without bevacizumab, the addition of bevacizumab does not appear to increase the blood clots.
- Patients who receive chemotherapy and bevacizumab have up to a 5% risk of developing a condition associated with "hardening of the arteries" such as stroke or heart attack. In studies, the risk of developing this condition was doubled in patients who received chemotherapy and bevacizumab. These medical conditions may be serious and can lead to death. The patients who were at even higher risk were 65 years of age or older or had a history of hardening of the arteries. If you develop one of these conditions, such as angina (heart pain), your treatment with bevacizumab will be discontinued.
- Severe high blood pressure or very low blood pressure which can cause a stroke
- Inflammation around the lining of the heart which can cause fluid to build up around the heart and give shortness of breath
- Weakening of the heart
- Infection
- Delayed wound healing or failure of previous wounds to heal
- Inflammation of the bowels causing diarrhea an stomach pain
- Inflammation of the throat making it hard to swallow
- Intestinal blockage requiring surgery
- Inflammation of the lungs which can cause shortness of breath
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS is a medical condition related to the leakiness of blood vessels in the brain and can cause confusion, blindness or vision changes, seizure or other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life-threatening and may have long-term effects on brain function.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study may affect an unborn baby. Women should not breast feed a baby while on this study because the drugs may affect an infant. Bevacizumab remains in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least 3-4 months after your last dose of bevacizumab, although the exact duration of bevacizumab remaining in the body is not predictable for each individual.
patient. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. While doctors hope that this treatment will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the treatment of locally advanced pancreatic cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?
Your other choices may include:
- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private? (7/29/05) (11/17/05)
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- The Radiation Therapy Oncology Group
- The Institutional Review Board of your hospital
- Qualified representatives of Genentech
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

What are the costs of taking part in this study?
You and/or your health plan/insurance company will need to pay for some or all of the costs of
treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The Division of Cancer Treatment, and Diagnosis, NCI will provide you with the NCI sponsored/supplied agent(s) free of charge for this study. Every effort will be made to ensure adequate supplies of the sponsored/supplied agent(s), free of charge, for all participants. If the drug becomes commercially available for this indication there is a remote possibility that you may be asked to purchase subsequent supplies. Your physician will discuss this with you should this situation arise.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at __________________ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ (telephone number).

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

**Consent Form for Use of Tissue for Research**

**About Using Tissue for Research**

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" at http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf to learn more about tissue research.

Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

**Things to Think About**

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research. Your tissue can be destroyed or returned to your institution.

In the future, people who do research may need to know more about your health. While the your doctor and/or institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.
Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
   Yes          No

2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
   Yes          No

3. Someone may contact me in the future to ask me to take part in more research.
   Yes          No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/
You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

Date _____________________________________
APPENDIX II

ZUBROD PERFORMANCE SCALE

0  Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1  Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2  Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3  Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4  Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

5  Death (Karnofsky 0)

KARNOFSKY PERFORMANCE SCALE

100  Normal; no complaints; no evidence of disease

90   Able to carry on normal activity; minor signs or symptoms of disease

80   Normal activity with effort; some sign or symptoms of disease

70   Cares for self; unable to carry on normal activity or do active work

60   Requires occasional assistance, but is able to care for most personal needs

50   Requires considerable assistance and frequent medical care

40   Disabled; requires special care and assistance

30   Severely disabled; hospitalization is indicated, although death not imminent

20   Very sick; hospitalization necessary; active support treatment is necessary

10   Moribund; fatal processes progressing rapidly

0    Dead
APPENDIX III

STAGING FOR PANCREAS
AJCC, 6th Edition

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ*
T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

* This also includes the "PanInIII" Classification

Stage Grouping

Stage 0 Tis N0 M0
Stage IA T1 N0 M0
Stage IB T2 N0 M0
Stage IIA T3 N0 M0
Stage IIB T1-3 N1 M0
Stage III T4 Any N M0
Stage IVB Any T Any N M1
NEW YORK HEART ASSOCIATION
Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*

Class I
Functional Capacity
Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Objective Assessment: No objective evidence of cardiovascular disease.

Class II
Functional Capacity
Patients with cardiac disease resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Objective Assessment: Objective evidence of minimal cardiovascular disease.

Class III
Functional Capacity
Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Objective Assessment: Objective evidence of moderately severe cardiovascular disease.

Class IV
Functional Capacity
Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Objective Assessment: Objective evidence of severe cardiovascular disease.

## APPENDIX V
### PATIENT’S PILL DIARY

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<th>Date</th>
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<th>P.M.: # of pills taken</th>
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<th>P.M.: # of pills taken</th>
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Patient’s Signature: ________________________________ Date: ____________________

**Physician’s Office will complete this section:**

1. Please indicate which month of treatment is indicated on this form (1-36): ______________
2. Complete dates: Start date ______________ End date ______________
3. Total number of pills taken this month ______________

Physician/Nurse/Data Manager’s Signature ________________________________
### APPENDIX VI

**Capecitabine Dosing Table Based Upon BSA**

Capecitabine 825 mg/m² BID. Only the 500 mg tablets will be utilized.

<table>
<thead>
<tr>
<th>BSA</th>
<th>Total Daily Dose (mg)</th>
<th>AM (mg)</th>
<th>PM (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.24</td>
<td>2000</td>
<td>1000</td>
<td>1000</td>
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<tr>
<td>1.25-1.36</td>
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<td>1000</td>
<td>1000</td>
</tr>
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<td>1.37-1.51</td>
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</tr>
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<td>1.52-1.64</td>
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</tr>
<tr>
<td>1.65-1.76</td>
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<td>1500</td>
</tr>
<tr>
<td>1.77-1.91</td>
<td>3000</td>
<td>1500</td>
<td>1500</td>
</tr>
<tr>
<td>1.92-2.04</td>
<td>3500</td>
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</tr>
<tr>
<td>&gt;2.18</td>
<td>3500</td>
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</table>

Capecitabine 25% dose reduction:
Capecitabine 619 mg/m² BID. Only the 500 mg tablets will be utilized.

<table>
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<th>Total Daily Dose (mg)</th>
<th>AM (mg)</th>
<th>PM (mg)</th>
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<tr>
<td>&lt; 1.24</td>
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<tr>
<td>1.25-1.36</td>
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<td>1.77-1.91</td>
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<td>1.92-2.04</td>
<td>2500</td>
<td>1500</td>
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</tr>
<tr>
<td>&gt;2.18</td>
<td>2500</td>
<td>1500</td>
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</tbody>
</table>

Capecitabine 50% dose reduction:
Capecitabine 412 mg/m² BID. Only the 500 mg tablets will be utilized.

<table>
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<th>Total Daily Dose (mg)</th>
<th>AM (mg)</th>
<th>PM (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.24</td>
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<tr>
<td>1.25-1.36</td>
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