RADIATION THERAPY ONCOLOGY GROUP

RTOG 1102

A PHASE I STUDY OF INDUCTION GANITUMAB (IND #113278) AND GEMCITABINE, FOLLOWED BY GANITUMAB, CAPECITABINE, AND 3D-CONFORMAL RADIATION THERAPY (3D-CRT) WITH SUBSEQUENT MAINTENANCE THERAPY FOR LOCALLY ADVANCED PANCREATIC CANCER

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(11/15/2011)

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A PHASE I STUDY OF INDUCTION GANITUMAB (IND #113278) AND GEMCITABINE, FOLLOWED BY GANITUMAB, CAPECITABINE, AND 3D-CONFORMAL RADIATION THERAPY (3D-CRT) WITH SUBSEQUENT MAINTENANCE THERAPY FOR LOCALLY ADVANCED PANCREATIC CANCER

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<tr>
<td>Ganitumab, 12 mg/kg q 14 days, and gemcitabine weekly for 3 weeks, followed by 1 week off until disease progression</td>
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* Pancreas protocol diagnostic CT (Appendix V) must be used for radiation planning
† Dose to be assigned at registration. See Section 7.1 for complete details.
See Section 5.0 for pre-registration requirements, Section 6.0 for details of radiation therapy, and Section 7.0 for details of drug therapy.

**Patient Population:** (See Section 3.0 for Eligibility)
Pathologically confirmed (histologic or cytologic), locally advanced adenocarcinoma of the pancreas.

**Required Sample Size:** Maximum of 42 patients
1. Does the patient have a pathologically confirmed (histologic or cytologic), locally advanced adenocarcinoma of the pancreas?  

2. Does the patient have unresectable disease based on the institution’s standardized criteria of unresectability or medical inoperability?  

3. Is the patient’s Zubrod Performance Status 0-1 within 7 days of study entry?  

4. Is the patient ≥ 18 years of age?  

5. Has the patient had prior systemic chemotherapy for pancreatic cancer?  

6. Has the patient had previous chemotherapy for malignancy other than pancreatic cancer?  
   (Y) If yes, was the chemotherapy completed > 3 years prior to study entry?  

7. Can the patient swallow oral medications?  

8. Was a history/physical examination, including collection of weight and vital signs done within 28 days prior to study entry?  

9. Was an abdominal/pelvic CT scan with IV contrast or MRI done within 21 days prior to study entry?  

10. Was a CT scan or whole-body PET/CT done within 21 days prior to study entry?  

11. Does the patient have adequate bone marrow, hepatic, and renal function a blood glucose level < 160 mg/dl and a HgbA1C < 8% as specified in Section 3.1?  

12. Is the patient, male or female, of reproductive potential?  
   (Y/N) If yes, is the patient sexually active?  
   (Y) If yes, will a medically acceptable form of contraception be used as specified in Section 3.2?  

13. For female patient, was a serum pregnancy test negative within 14 days prior to study entry?  

14. Did the patient provide study-specific informed consent prior to study entry?  

15. If the patient requires oral anticoagulants, will the patient’s INR be monitored?  

16. Is there evidence of distant metastatic disease, second malignancy or peritoneal seeding at the time of study entry?  

17. Has the patient had prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?  

18. Does the patient have severe, active co-morbidity, as defined in Section 3.2.6?
19. Is the patient pregnant or lactating as specified in Section 3.2? (N)

20. Has the patient had a prior invasive malignancy? (Y/NA)
   - If yes, has the patient been disease free for a minimum of 3 years? (Y)

21. Has the patient had a prior allergic reaction to capecitabine or gemcitabine? (N)

22. Prior treatment with IGF-1R inhibitor? (N)

23. Will the patient be participating in another clinical treatment trial while on study? (N)

24. Does the patient have existing venous thromboembolism requiring anti-coagulation treatment? (N)

25. Does the patient have hearing impairment (grade 2 or worse auditory impairment)? (N)

The following questions will be asked at Study Registration:

3D-CRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

1. Institutional person randomizing case.
2. Has the Eligibility Checklist been completed? (Y)
3. In the opinion of the investigator, is the patient eligible? (Y)
4. Date informed consent signed
5. Patient’s Initials (First Middle Last)
6. Verifying Physician
7. Patient ID
8. Date of Birth
9. Race
10. Ethnicity
11. Gender
12. Country of Residence
13. Zip Code (U.S. Residents)
14. Method of Payment
15. Any care at a VA or Military Hospital?
16. Calendar Base Date
17. Randomization date
18. Medical oncologist’s name
Have you obtained the patient’s consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

Have you obtained the patient’s consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

Have you obtained the patient’s consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer’s disease, and heart disease)?

Have you obtained the patient’s consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).

Have you obtained the patient’s consent to allow someone from this institution to contact him or her in the future to take part in more research?

The Eligibility Checklist must be completed in its entirety prior to web registration. 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 Rationale for Selected Approach and Trial Design

1.1.1 Locally Advanced Pancreatic Cancer

Of the 43,140 patients diagnosed with pancreatic carcinoma in the United States this year, approximately 40% will present with locally advanced disease (Jemal 2010). These patients have pancreatic tumors that are surgically unresectable due to encasement or occlusion of the superior mesenteric vein (SMV), SMV/portal vein confluence, or direct involvement of the superior mesenteric artery (SMA), celiac axis, inferior vena cava, or aorta. Radiotherapeutic approaches are often utilized for these patients (Willett 2005).

1.1.2 Chemoradiation for Locally Advanced Pancreatic Cancer

The Mayo Clinic undertook an early randomized trial in the 1960s in which 64 patients with surgically staged locally unresectable, non-metastatic pancreatic adenocarcinoma received 35 to 40 Gy of radiation and concurrent fluorouracil (5-FU/RT) versus radiation alone. A significant survival advantage was seen for patients receiving 5-FU/RT (10.4 months vs. 6.3 months, respectively) (Moertel 1969). The Gastrointestinal Tumor Study Group (GITSG) followed with a similar study comparing RT alone to 5FU/RT and maintenance 5-FU. A survival benefit was demonstrated with the combined modality arm (Moertel 1981).

A follow-up GITSG trial compared chemotherapy alone to chemoradiotherapy in surgically confirmed unresectable tumors. Forty-three assessable patients were randomly assigned to receive combination streptozocin, mitomycin, and 5-FU (SMF) chemotherapy or 5-FU/XRT followed by adjuvant SMF chemotherapy. The chemoradiotherapy arm demonstrated a significant survival advantage over the chemotherapy-alone arm (1-year survival, 41% vs. 19%) (GITSG 1988).

In contrast to the results of the studies discussed above, the Eastern Cooperative Oncology Group (ECOG) reported no benefit to chemoradiotherapy versus chemotherapy only (Klaassen 1985). In the ECOG study, patients with unresectable, non-metastatic pancreatic or gastric adenocarcinoma were randomly assigned to receive either 5-FU chemotherapy alone or 40 Gy external beam RT with concurrent bolus 5-FU on week 1. No survival difference was observed between the two groups (median survival, 8.2 vs. 8.3 months) (Klaassen 1985). The ECOG trial E4201 demonstrated a survival benefit of gemcitabine and concurrent radiation as compared to gemcitabine alone (Loehrer 2008).

Continuous-infusion 5-FU allows for increased cumulative drug dose and a more protracted radiosensitization relative to bolus 5-FU. Phase I and phase II trials have been performed in pancreatic cancer, showing that the use of infusional 5-FU is without excessive treatment-related toxicity and is effective (Whittington 1995; Bo 2001; Osti 2001). Continuous oral dosing of capecitabine simulates a continuous 5-FU infusion (Ben-Josef 2004; Vaishampayan 2002). Phase II studies of capecitabine/RT appear to have equivalent outcomes to continuous infusion 5-FU, although a randomized study has not been performed (Dunst 2002).

The RTOG and other cooperative groups have tested other radiation sensitizers for locally advanced pancreatic cancer. For example, RTOG 98-12 evaluated weekly paclitaxel x 6 treatments with 50.4 Gy radiation in 109 patients (Rich 2004). A median survival of 11.2 months was achieved. RTOG PA-0020 evaluated weekly paclitaxel (50 mg/m²) and low-dose gemcitabine (75 mg/m²) for 6 weeks with concurrent 50.4 Gy radiation with and without the farnesyl transferase inhibitor R115777 (Rich 2006). The control arm of chemoradiation alone had a median survival of 12 months in 84 patients.

RTOG 0411 investigated the addition of bevacizumab to capecitabine and radiation followed by gemcitabine. Between January 2005 and February 2006, 94 patients with locally advanced, non-metastatic, unresectable pancreatic cancer without endoscopic or radiographic evidence of duodenal invasion were treated with 50.4 Gy in 28 fractions of radiotherapy with concurrent capecitabine (825 mg/m² orally twice daily on days of...
radiation) and bevacizumab at 5 mg/kg on days 1, 15, and 29. Patients with stable or responding disease 4 weeks after chemoradiation were continued on maintenance gemcitabine (1 gm IV every week x 3) and bevacizumab (5 mg/kg every 2 weeks) in 4-week cycles until progression. The median and 1-year overall survival was 11.9 months (CI 10.1, 14.2) and 47% (CI 45-57). Median progression-free survival was 9.4 months (CI 7.8, 0.6). A median of 3 cycles of maintenance chemotherapy was given. Overall, 37.8% of patients had grade 3 or greater treatment-related gastrointestinal (GI) adverse events (18.3% during chemoradiation and 19.8% during maintenance chemotherapy), and 52% patients experienced ≥ grade 3 adverse events.

Pattern of progression and promising single-institution outcome data have led to a consensus among the pancreatic cancer task force that induction chemotherapy followed by consolidation chemoradiation be considered the standard approach. To date, no multi-institutional trial has demonstrated a median survival of greater that 12 months using either an initial chemoradiation or an induction chemotherapy approach.

1.1.3 IGF-1R and Cancer
The insulin-like growth factor receptor type 1 (IGF-1R) is a ubiquitously expressed type 1 transmembrane receptor tyrosine kinase. IGF-1R plays an important role in regulating cell proliferation and apoptosis (Blume-Jensen 2001). The binding of the ligands insulin-like growth factor types 1 and 2 (IGF-1 and IGF-2) induces receptor phosphorylation and subsequent tyrosine phosphorylation of insulin receptor substrate 1 and src-and collagen-homology protein. This results in the activation of PI3-kinase/Akt, Ras/MAP kinase, and JAK/STAT pathways regulating cell proliferation and survival (Surnac 2003).

The IGF-1R pathway may play a role in the pathobiology of many human cancers (Pollak 2004). In transgenic mouse models, tumor incidence is associated with elevated IGF-1 expression (Bol 1997; DiGiovanni 2000; Hadsell 2000). The IGF-1R pathway provides a target for the treatment of cancers. In animal models of cancer, inhibiting the IGF-1R pathway with receptor-blocking antibodies or small molecules inhibits the growth of human xenograft tumors and enhances the cytotoxicity of chemotherapy and radiation therapy. (Mitsiades 2004; Goetsch 2005; Cohen 2005).

1.1.4 IGF-1R and Pancreatic Cancer
The potential of inhibiting IGF-1R signaling in models of pancreatic cancer has been extensively reported (Bergmann 1995; Min 2003; Ohmura 1990; Tanno 2001, Neid 2004; Stoeltzing 2003). IGF-1R and its ligands IGF-1 and IGF-2 are expressed in pancreatic carcinoma tumor cells and the surrounding stroma. Pancreatic cancer cell lines such as PAC-1, BxPC-3, AsPC-1, and MiaPaCa are responsive to IGF-induced growth. Inhibition of IGF-1R results in decreased survival and reduced of proliferation in these cell lines (Amgen Investigator Brochure).

1.1.5 IGF-1R Inhibitors Enhance Radiation
There is strong rationale to combine IGF-1R inhibitors with radiation. Increased signaling through IGF-1R is associated with resistance to radiation in preclinical studies. For example increased IGF-1R signaling leads to radiation resistance in fibroblasts, which can be overcome by antisense oligonucleotides against IGF-1R (Turner 1997). IGF-1R inhibitors sensitize human SW480 to radiation (Yavari 2010). Sensitivity to radiation increases when the IGF-1R gene is silenced in response to siRNA knockdown (Rochester 2005). In clinical patient studies, local recurrence of breast cancer after radiation is associated with IGF-1R expression (Turner 1997).

1.1.6 Ganitumab: Phase I Studies
Ganitumab is a fully human, monoclonal antibody antagonist of IGF-1R. A phase I study of ganitumab was performed to determine the maximum-tolerated dose (MTD) and to assess the safety, pharmacokinetics, and evidence of antitumor activity (Tolcher 2004). Fifty-three patients received 312 infusions of ganitumab every 2 weeks. Overall, the most common grades 1 to 2 toxicities were fatigue, thrombocytopenia, fever, rash, chills, and anorexia. One dose-limiting toxicity (grade 3 thrombocytopenia) occurred in a patient at 20 mg/kg during course 1. The maximum-planned dose of 20 mg/kg was safely administered; thus, an MTD was not reached. High levels of neutrophil IGF-1R binding were observed in the 12- and 20-mg/kg cohorts. Tumor responses included one
durable complete response (CR) and one unconfirmed partial response (PR) in 2 patients with Ewing/primitive neuroectodermal tumors; 1 pr and 1 minor response occurred in 2 patients with neuroendocrine tumors. The patients with Ewing/PNET who had a complete response remained disease free on therapy after 28 months. Therefore, this study demonstrated that ganitumab can be administered safely at 20 mg/kg IV every 2 weeks without significant toxicities with the ability to attain high levels of IGF-1R binding.

A phase I study of ganitumab with gemcitabine for patients with advanced solid tumors was reported (Sarantopoulos 2008). Significant adverse events included hyperglycemia in 10% of patients and increase in hepatic transaminases in 13% of patients. A phase II dose level of gemcitabine 1 gm/m² week 3 of 4 weeks and ganitumab 12 mg/kg every 14 days was chosen for further study.

1.1.7 Randomized Phase II Study of Ganitumab Plus Gemcitabine in Pancreatic Cancer

A 3-arm randomized phase II study involving ganitumab and gemcitabine has been completed in 120 patients with metastatic pancreatic cancer. In arm 1 patients received gemcitabine and AMG 655 (a TRAIL receptor agonist antibody). In arm 2 patients received gemcitabine and ganitumab. Arm 3 was gemcitabine alone. The percentage of patients with grade 3/4 adverse events (arms 1/2/3) included: neutropenia 22%/18%/13%; thrombocytopenia 17%/15%/8%; abdominal pain 17%/8%/13%; fatigue 12%/13%/5%; and hyperglycemia 2%/18%/3%. Therefore, hyperglycemia was the most significant toxicity associated with the addition of ganitumab to gemcitabine. The arm of ganitumab and gemcitabine was the most promising. Ganitumab plus gemcitabine versus gemcitabine tended toward improved 6-month overall survival (57% vs 50%), 12-month overall survival (39% vs 23%), median overall survival (8.7 vs 5.9 month), and median progression-free survival (5.1 vs 2.1 month) (Kindler 2010). These data suggest that further study of ganitumab plus gemcitabine is warranted in pancreatic cancer.

1.1.8 Ganitumab dose

Lu et al (2011) described an exposure-response analysis to facilitate phase III dose selection for ganitumab in combination with gemcitabine to treat metastatic pancreatic cancer. Ganitumab PK was estimated via a population PK model. In patients treated on the randomized phase II ganitumab + gemcitabine versus gemcitabine study, the effect of estimated steady-state area under the curve (AUCₚ) on overall and progression free survival and progression free survival was evaluated with a Cox proportional hazard model. There was a positive association between overall survival and progression free survival and higher AUCs in the ganitumab+gemcitabine arm (P<0.001, <0.001). The incidence of most adverse events was similar between the AUCs < and ≥ median groups, although grade ≥3 hyperglycemia and thrombocytopenia trended higher in pts with AUCs ≥ median. Hepatic toxicity was more frequent in pts with AUCs < median. No gemcitabine/ganitumab PK interactions were identified. Clinical trial simulations projected improved OS and PFS with 20 vs 12 mg/kg ganitumab. Based on these findings, these data were used to for dose selection for the ongoing randomized phase 3 study in which 12 and 20 mg/kg ganitumab with gemcitabine will be evaluated against gemcitabine alone and supports the evaluation of dosing up to 20mg/kg with capecitibine and radiation in this RTOG study. Based on the randomized phase II study, the ganitumab dose of 12mg/kg will be administered with gemcitabine before and after chemoradiation.

1.1.9 Protocol Overview

Conventional treatment for locally advanced pancreatic cancer is unsatisfactory; systemic and locoregional progressions are common. An effective new agent must enhance chemoradiation and improve systemic activity. As described above, IGF-1R inhibitors are radiation sensitizers. Following the promising randomized phase II study, Amgen is conducting a phase III trial of ganitumab in metastatic pancreatic cancer. If this metastatic trial is positive, incorporating ganitumab in a randomized trial, such as a randomized phase II trial for patients with locally advanced disease, would be indicated. However, the safety of ganitumab with chemoradiation must first be assessed. The proposed phase I trial will provide the necessary safety data for the
RTOG to investigate ganitumab in a randomized trial in locally advanced pancreatic cancer (if the Amgen metastatic study is positive).

All patients will first receive 2 months of induction chemotherapy with gemcitabine and ganitumab. Induction chemotherapy is favored prior to chemoradiation to provide early optimal systemic treatment and also to select patients most likely to benefit from chemoradiation (Krishnan 2007; Huguet 2007). Previous RTOG studies, such as RTOG 0411, have shown no increase in toxicity during chemoradiation when induction chemotherapy is first administered. Following induction chemotherapy, patients will receive ganitumab, investigating doses of (12mg/kg and 20 mg/kg with capecitabine (825 or 625mg/m^2) and standard radiation.

2.0 OBJECTIVES
2.1 Primary Objective
To evaluate the maximum dose of ganitumab, up to a target dose of 20 mg/kg, given concurrently with capecitabine and radiation following induction ganitumab and gemcitabine for patients with locally advanced pancreatic cancer.

2.2 Secondary Objectives
2.2.1 To evaluate the safety profile for patients with locally advanced pancreatic cancer treated with induction ganitumab and gemcitabine, followed by ganitumab and concurrent chemoradiation and subsequently followed by maintenance ganitumab and gemcitabine until disease progression.
2.2.2 To evaluate response and overall survival for patients treated at the maximum dose of ganitumab given concurrently with capecitabine and radiation following induction ganitumab and subsequently followed by maintenance ganitumab and gemcitabine until disease progression.

3.0 PATIENT SELECTION
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED
3.1 Conditions for Patient Eligibility
3.1.1 Pathologically confirmed (histologic or cytologic), locally advanced, adenocarcinoma of the pancreas; patients must have unresectable disease based on institutional standardized criteria of unresectability or medical inoperability.
3.1.2 Patients with and without regional adenopathy are eligible.
3.1.3 No distant metastases, based upon the following minimum diagnostic workup:
3.1.3.1 History/physical examination, including collection of weight and vital signs within 28 days prior to study entry;
3.1.3.2 Abdominal/pelvic CT scan with IV contrast or MRI scan within 21 days prior to study entry;
3.1.3.3 Chest CT or whole-body PET/CT within 21 days prior to study entry.
3.1.4 Zubrod performance status 0-1 within 7 days of study entry.
3.1.5 Age ≥ 18.
3.1.6 Serum chemistries and CBC w/ differential, platelets, and automated granulocyte count within 14 days prior to study entry, as follows.
3.1.6.1 Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
3.1.6.2 Platelets ≥ 100,000 cells/mm^3;
3.1.6.3 Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.);
3.1.6.4 Serum creatinine ≤ 1.5 mg/dl;
3.1.6.5 ALT or AST < 3 x upper limit of normal;
3.1.6.6 Total bilirubin < 3.0 mg/dL;
3.1.6.7 Alkaline phosphatase < 3 x upper limit of normal;
3.1.6.8 Blood glucose level ≤ 160 mg/dL (8.9 mmol/L) and a HgbA1C ≤ 8%. Subjects with a non-fasting blood glucose > 160 mg/dL (8.9 mmol/L) must have a fasting blood glucose ≤ 160 mg/dL (8.9 mmol/L) in order to be eligible”.
3.1.7 Negative serum pregnancy test (if applicable) within 14 days prior to study entry.
3.1.8 Ability to swallow oral medications.
3.1.9 Patients requiring oral anticoagulants (e.g., Coumadin, warfarin) are eligible provided there is increased vigilance with respect to monitoring INR. If medically appropriate and treatment is available, the investigator may also consider switching these patients to low molecular weight heparin, as an interaction with capecitabine is not expected (See Section 9.1).

3.1.10 Patient must provide study specific informed consent prior to study entry.

3.1.11 Women of childbearing potential and male participants who are sexually active must practice adequate contraception.

3.2 Conditions for Patient Ineligibility

3.2.1 Distant metastatic disease, second malignancy or peritoneal seeding;

3.2.2 Prior invasive malignancy (except non-melanomatus skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.2.3 Prior systemic chemotherapy for pancreatic cancer; Note: previous chemotherapy for malignancies other than pancreatic cancer is allowed, provided that chemotherapy was completed > 3 years prior to study entry.

3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.5 Any major surgery within 28 days prior to study entry (for example, insertion of a vascular access device, insertion of a biliary stent, exploratory laparotomy, and laparoscopy are not considered major surgery);

3.2.6 Severe, active co-morbidity, defined as follows:

3.2.6.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;

3.2.6.2 Transmural myocardial infarction within 6 months prior to study entry;

3.2.6.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;

3.2.6.4 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration;

3.2.6.5 Uncontrolled malabsorption syndrome significantly affecting gastrointestinal function;

3.2.6.6 Any unresolved bowel or bile duct obstruction;

3.2.6.7 Major resection of the stomach or small bowel that could affect the absorption of capecitabine;

3.2.6.8 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 patients receiving antiretroviral therapy may experience possible pharmacokinetic interactions with capecitabine.

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception during the course of the study and for women, for 3 months after the last study drug administration and for men, for 6 months after the last study drug administration; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Women who are lactating at the time of registration and who plan to be lactating through 3 months after the last study drug administration.

3.2.9 Prior allergic reaction to capecitabine or gemcitabine

3.2.10 Prior treatment with IGF-1R inhibitor;

3.2.11 Participation in another clinical treatment trial while on study.

3.2.12 Existing VTE requiring anti-coagulation therapy.

3.2.13 Hearing impairment (Grade 2 or worse)
4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.1.1 Patients with biliary or gastroduodenal obstruction must have biliary stent placement or surgical bypass prior to study entry. If a gastric or biliary bypass is performed, it must be performed at least 28 days prior to study entry.

4.1.2 Electrolytes—Na, K, Cl, Mg, CO2—and CA 19-9 within 14 days prior to study entry.

4.1.3 Documentation of history of hearing loss within 28 days prior to study entry.

NOTE: patients with grade 2 or worse hearing loss at the time of study entry will not be eligible.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements for 3DCRT Treatment Approach

5.1.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients onto this study.

5.1.2 The new Facility Questionnaire (one per institution, available on the ATC website at http://atc.wustl.edu) is to be sent to RTOG for review prior to entering any cases. If the institution has already completed a Facility Questionnaire then the institution may request a copy of it from RTOG Headquarters to simply update the questionnaire and resubmit the updated Facility Questionnaire to the RTOG. Upon review and successful completion of a “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

5.2 Regulatory Pre-Registration Requirements (NOTE: This study is not open to non-U.S. institutions.)

5.2.1 U.S. institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/public/CTSU-IRBcertif_Final.pdf. The study related regulatory documentation may also be e-mailed to the CTSU at CTSURegulatory@ctsu.Coccg.org. This must be done prior to registration of the institution’s first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)

*Note: Institutions must provide certification of consent translation to RTOG Headquarters

5.2.2 Pre-Registration Requirements for the Initial Shipment of Ganitumab

All pre-registration requirements must be met before registering the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG website, www.rtog.org, under protocol-specific materials/regulatory resources. U.S. institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

5.3 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG website. To get a user name and password:
The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).

A representative from the institution must complete the Password Authorization Form at http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219 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 Logon” 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.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) Is Not Allowed

This protocol requires a Rapid Review PRIOR TO DELIVERY of radiation treatment. This Rapid Review is aimed at providing feedback from the study Principal Investigators on the institution’s contours and treatment plan. In order to accomplish this Rapid Review, digital data must be submitted in a timely fashion (see Section 6.6 below for details). Three business days are required to complete the Rapid Review.

Protocol radiation treatment must begin no sooner than 10 days and within 28 days after the last chemotherapy dose. A pancreatic protocol CT (Appendix V) must be obtained for treatment planning.

6.1 Dose Specifications

6.1.1 Primary Tumor and regional lymphatic target

The primary tumor and any clinically enlarged lymph nodes will be treated with no intent to treat nodal regions prophylactically. Total dose will be prescribed to give 95%
coverage of the PTV as defined in Section 6.4 and will be 50.4 Gy in 28 fractions over 5.5 weeks (1.8 Gy/1 day). The minimum dose within the PTV must not fall below 97% of the prescribed dose. The maximum dose within the PTV must not exceed 110% of this dose. Variations from these maximum and minimum values are given in Section 6.7.

6.2 Technical Factors

Equipment: Photons of at least 6 MV will be used. A minimum of 3 or 4 field conformal plans are required with customized beam angles and weighting.

6.3 Localization, Simulation, and Immobilization

6.3.1 Treatment Planning Simulation
Treatment planning must be conducted after performing a pancreatic protocol diagnostic CT (see Appendix V). In order to optimize target delineation, the diagnostic images must be fused with the planning CT, or intravenous contrast must be used at the time of simulation unless there is renal insufficiency or iodine allergy. In case intravenous contrast is not used, an MRI scan should be obtained if possible (see Appendix V) and fused with the simulation images. Whether or not intravenous contrast is used, oral contrast (VoLumen is recommended) must be used at time of simulation.

Planning scan slice thickness must be no greater than 3 mm. In order to complete the Rapid Review process, these images must be uploaded to the Image-Guided Therapy QA Center Database (ITC, Washington University, St. Louis) as part of the QA process no later than 14 days prior to the start of radiation treatment (see Section 6.6 for more details).

The protocol planning CT imaging and dosimetry plans must be submitted and reviewed prior to the start of radiation treatment by the Principal Investigator, Dr. Crane, or the Radiation Oncology Co-Chair, Dr. Herman.

Patients will be simulated (and treated) supine with arms up. Immobilization is required. A thorax board is recommended.

6.3.2 Set-Up Verification
Orthogonal images must be obtained on the first day of treatment for set-up verification and weekly thereafter. Either kilovoltage (kV) or megavoltage (MV) imagers may be used. IGRT techniques can be used for daily imaging, but they will not be collected. Also, the use of IGRT cannot be used as a justification of the reduction of the margins described in Section 6.4. The patient should be aligned based on the vertebral bodies adjacent to the PTV.

6.4 Treatment Planning/Target Volumes
The recommended treatment plan for this protocol is a customized 3-D plan. At least 3 fields are required and 4 fields are recommended. The PTV can be covered with any set of beam angles and customized weighting. The suggested starting point in the planning process is AP/PA with opposed lateral fields. Often if the right kidney dose is too high (>50% exceeding 18Gy), removing the PA beam and reoptimizing the weighting with wedges will lower the right kidney dose. The dosimetric plan must be submitted at least 2 weeks prior to the start of treatment.

6.4.1 Volume Definitions

6.4.1.1 The GTV will include the primary tumor and regional adenopathy > 10mm on the pretreatment pancreatic protocol CT.

6.4.1.2 The CTV is defined as the GTV plus a 10 mm expansion for microscopic extension in regions at risk (e.g., vertebral body to be excluded). Uninvolved regional nodes will NOT be included in the CTV.

6.4.1.3 The PTV is defined as the CTV plus a 20 mm expansion in the cranial and caudal directions and a 10 mm expansion in the radial (lateral, anterior and posterior and oblique dimensions).

6.4.1.4 The normal structures to be contoured are: left and right kidneys, liver, stomach, duodenum, spinal cord.
Contour the kidneys, liver, stomach and duodenum in their entireties and any jejunum that is within 5 cm of the PTV.

### Required Critical Structure Definition and Normal Tissue Dose-Volume Constraints
(The structures listed in the table below must be contoured and the constraints listed can be used for treatment planning purposes.)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney (L &amp; R)</td>
<td>Not more than 30% of the total volume can receive ≥ 18 Gy. If only one kidney is functional, not more than 10% of the volume can receive ≥ 18 Gy.</td>
</tr>
<tr>
<td>Stomach, duodenum, jejunum</td>
<td>Max dose 55 Gy</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean dose cannot exceed 30 Gy</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Max dose to a volume of at least 0.03 cc must be ≤ 45Gy</td>
</tr>
</tbody>
</table>

### Documentation Requirements

#### Quality Assurance Documentation
The CT-simulation images along with target and critical structure contours and the treatment plan must be digitally sent to the ITC (See Section 12.2). The imaging and dosimetry plans will be reviewed PRIOR TO DELIVERY of radiation treatment by the Principal Investigator, Dr. Crane, or the Radiation Oncology Co-Chair, Dr. Herman. In order to complete this Rapid Review process, the required information must be received at the ITC at least 14 days before the start of radiation treatment. To accomplish this, patients should be simulated and planned during the second cycle of chemotherapy.

#### Pancreas protocol CT scan and/or MRI showing the extent of the tumor with contrast; the treatment plan (simulation images, structure set, dose volume histograms) must be uploaded to the Image-Guided Therapy QA Center Database.

#### Treatment Interruptions
Treatment interruptions should be clearly documented in the patient’s treatment record. If the sum total exceeds 10 break days, the treatment will be considered Deviation Unacceptable.

### Compliance Criteria
The Rapid Review process for this protocol is aimed at avoiding incorrect contouring of target and critical structures for this protocol.

#### Volume Definitions

#### Per Protocol: See Section 6.1.1

#### Variation acceptable
- Minimum dose within the PTV is less than 97% of the prescribed dose, but does not fall below 93% of this dose
- Maximum dose within the PTV is greater than 110% of the prescribed dose, but does not exceed 115% of this dose

#### Deviation Unacceptable
- Minimum dose within the PTV falls below 93% of the prescribed dose
- Maximum dose goes above 115% of the prescribed dose
- Incomplete contouring of the entire GTV or PTV
- Use of different margins than specified in Section 6.4.2 for the CTV and PTV
- Over contouring of the GTV by > 30 cc (15 cc if it results in inclusion of extra duodenum, small intestine, or stomach)
- Incorrect contouring of the duodenum, stomach, or small intestine that results in > 15 cc in overlap of the PTV with the OAR.
6.7.1.4 Elapsed Days

- Per Protocol – No break days
- Variation Acceptable – Up to 9 break days
- Deviation Unacceptable – More than 10 break days

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

6.7.2 Compliance Criteria for Critical Structures

The compliance criteria for the critical structures identified for this protocol are based on the planning constraints presented in Section 6.5.

6.7.2.1 Kidneys:

- Per protocol: the requirements in Section 6.5 are fulfilled
- Variation Acceptable: If two kidneys are functional, >30% but < 40% of total kidney volume receives ≥ 18 Gy. If one kidney is functional, >10% but < 20% of total kidney volume receives ≥ 18 Gy.
- Deviation Unacceptable: If two kidneys are functional, ≥ 40% of total kidney volume receives ≥ 18 Gy. If one kidney is functional, ≥ 20% of total kidney volume receives ≥ 18 Gy.

6.7.2.2 Spinal cord:

- Per protocol: the requirements in Section 6.5 are fulfilled
- Variation Acceptable: None
- Deviation Unacceptable: Max dose > 45 Gy to a volume that is at least 0.03 cc.

6.7.2.3 Liver:

- Per protocol: the requirements in Section 6.5 are fulfilled
- Variation Acceptable: None
- Deviation Unacceptable: The mean liver dose exceeds 30 Gy

6.8 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chairs, Christopher Crane, MD, and Joseph Herman, MD, will perform rapid RT Quality Assurance Reviews for all enrolled cases. Rapid review and approval of RT planning will be conducted PRIOR TO DELIVERY of radiation treatment.

6.9 Radiation Therapy Adverse Events

6.9.1 Adverse Event (AE) and Dose Modification for Radiation

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Parameters</th>
<th>Agent</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>Grade 4 neutropenia or ≥ grade 3 platelets</td>
<td>RT</td>
<td>Blood work at least weekly; resume RT when ANC is ≥ 500 cells/μl and platelets ≥ 50,000 cells/μl</td>
</tr>
<tr>
<td>Clinically significant treatment related Nonhematologic toxicity</td>
<td>≥ grade 3</td>
<td>RT</td>
<td>Hold until AE has resolved to ≤ Grade 2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Grade 3: ≥ 7 stools over baseline or IVF &gt; 24 hr; hospitalization needed</td>
<td>RT</td>
<td>Hold until AE has resolved to ≤ grade 2</td>
</tr>
</tbody>
</table>

6.10 Radiation Therapy Adverse Event Reporting

See 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.

Protocol drug treatment must begin within 7 days from study entry.

7.1 Treatment

The specific dose level for each patient will be assigned at study registration.

Table A

<table>
<thead>
<tr>
<th>Induction ganitumab and gemcitabine</th>
<th>Ganitumab, 12 mg/kg q14 days, and gemcitabine, 1 gm/m²/week For 3 weeks and 1 week off for 2 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level -1</td>
<td>6 mg/kg 825 mg/m²/dose</td>
</tr>
<tr>
<td>Starting Dose Level 1</td>
<td>12 mg/kg 825 mg/m²/dose</td>
</tr>
<tr>
<td>Dose Level 2</td>
<td>20 mg/kg 825 mg/m²/dose</td>
</tr>
</tbody>
</table>

Maintenance

Ganitumab, 12 mg/kg q 14 days, and gemcitabine, 1 gm/m²/week for 3 weeks, followed by 1 week off until disease progression

Table B (if needed, see Section 13.2)

<table>
<thead>
<tr>
<th>Induction ganitumab and gemcitabine</th>
<th>Ganitumab, 12 mg/kg q14 days, and gemcitabine, 1 gm/m²/week for 3 weeks and 1 week off for 2 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level -1</td>
<td>6 mg/kg 825 mg/m²/dose</td>
</tr>
<tr>
<td>Starting Dose Level 1</td>
<td>12 mg/kg 625 mg/m²/dose</td>
</tr>
<tr>
<td>Dose Level 2</td>
<td>20 mg/kg 625 mg/m²/dose</td>
</tr>
</tbody>
</table>

Maintenance

Ganitumab, 12 mg/kg q 14 days, and gemcitabine, 1 gm/m²/week for 3 weeks, followed by 1 week off until disease progression

7.1.1 Induction Ganitumab and Gemcitabine

Prior to starting RT, patients will receive 2 cycles (2 months) of ganitumab and gemcitabine. One cycle is defined as ganitumab, 12 mg/kg, day 1 and 15, every 28 days and gemcitabine, 1 gm/m²/week (starting on day 1) for 3 weeks followed by 1 week off. Note: Since both the Ganitumab and Gemcitabine are given intravenously, Ganitumab should be given prior to gemcitabine.
7.1.2 Concurrent Ganitumab, Capecitabine, and RT (to start 10-28 days after the second cycle of induction ganitumab and gemcitabine)

Ganitumab is administered intravenously over 1 to 2 hours at the assigned dose every 14 days until radiation is completed (day 1, 15 and 29). Capecitabine is administered orally at the assigned dose (see table above) Monday through Friday on radiation days until radiation is completed. Patients will be allowed to take their first daily oral Capecitabine dose prior to their Ganitumab and radiation treatments. The latter dose may be taken after these treatments will be complete.

NOTE: See Sections 7.2.6 and 7.4.4 for administration instructions related to bone marrow, hepatic, and renal function.

It is recommended that patients be on a proton pump inhibitor during and for 1 month after radiation (See Section 9.1).

7.1.3 Post-Chemoradiation Ganitumab and Gemcitabine (to start between 21-42 days after completion of concurrent phase)

All clinically significant toxicities must resolve to ≤ grade 1. Patients will then receive intravenous ganitumab, 12 mg/kg q 14 days, and intravenous gemcitabine, 1 gm/m²/week for 3 weeks followed by 1 week off. Treatment will continue until disease progression or unacceptable toxicities. Similar to section 7.1.1, Ganitumab will be given prior to gemcitabine.

7.2 Ganitumab Agent Information (IND #113278) (4/23/127/26/12)

Efforts should be made to ensure that the study supplies used, preparation procedure, and conditions are consistent for each dose of ganitumab that is administered.

See Investigator Brochure for comprehensive information.

7.2.1 Investigator Brochure
Requests for Investigator Brochures should be e-mailed to:

Barbara Allen
Director, Clinical Development, Extramural Research
Phone: 805-447-3512
E-mail: ballen@amgen.com

7.2.2 Packaging and Formulations
Ganitumab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical trial investigational product distribution procedures via Fisher Pharmaceuticals.

Ganitumab will be presented as sterile, clear, colorless liquid in a 10 mL vial. The formulation for ganitumab is 70 mg/mL of ganitumab, formulated with 10 mM sodium acetate, 5.0% (w/v) sorbitol, 0.004% (w/v) polysorbate 20, pH 5.2. Each vial of ganitumab will contain approximately 10 mL of study medication. Vials are appropriately overfilled to ensure that a sufficient deliverable dose is provided, and each vial is intended for single use only. The diluent used in the intravenous bag is 0.9% (w/v) sodium chloride.

7.2.3 Labeling
Each vial of ganitumab will be labeled in accordance with current ICH GCP, food and drug administration and specific national requirements.

7.2.4 Storage
To ensure stability, ganitumab must be stored under the conditions specified below.
Ganitumab is shipped by courier in a controlled temperature (2°C to 8°C) container that is suitable for shipping biological substances. Ganitumab vials will arrive in secondary box packaging and should be immediately placed in a refrigerator maintained at 2°C to 8°C in a secured location until planned use. The set point for the refrigerator should be at 5°C.

<table>
<thead>
<tr>
<th>Refrigerator Set Point (°C)</th>
<th>Acceptable Parameters</th>
<th>Acceptable Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>5°C</td>
<td>(+/- 3°C)</td>
<td>2°C to 8°C</td>
</tr>
</tbody>
</table>

Ganitumab should be stored protected from light in a secure refrigerator prior to use. Ganitumab is stable if maintained in accordance with the guidelines described and the provided expiration date.

Records of the actual storage conditions during the period of the study must be maintained (e.g., records of the date and time and initials of person checking, and the “working day” temperatures of the refrigerator used for storage of study supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).

Do not:
- Shake the vials vigorously
- Deviate from the storage temperatures above
- Directly expose the IP to CO₂ or dry ice

Failure to follow the instructions above may lead to denaturation and inactivation of ganitumab.

Amgen should be notified via Amgen’s Temperature Excursion Form (located on the RTOG website under Regulatory Resources) if any ganitumab undergoes temperature excursions (temperatures outside 2°C to 8°C) or if vials become cracked or broken. This drug supply should not be utilized unless Amgen personnel have advised it is acceptable to do so.

7.2.5 Preparation

Preparation of ganitumab will be performed using aseptic technique.

Vigorous shaking of the vial or delivery via pneumatic systems (pressurized air tubes) must be avoided as it may cause the protein to denature from the solution.

Ganitumab IV will be prepared in 0.9% NaCl. Swab the injection port of the infusion bag or bottle and slowly inject the total volume of ganitumab. The IV bag or bottle should be gently massaged or turned with both hands to thoroughly mix the solution. Do not shake the bag or bottle. Once ganitumab has been diluted/mixed into the 0.9% NaCl it must be infused within 6 hours.

When preparing ganitumab, the final concentration should be between 0.60 mg/mL to 20 mg/mL. For doses lower than 2000 mg (up to 28.5 mL) dilute the IP to a total volume of 100 mL with 0.9% sodium chloride in the IV bag. Doses higher than 2000 mg (≥ 28.6 mL) can be administered in larger volume bags (eg, 150 or 250 mL bags) with 0.9% sodium chloride.

All prepared IV bags and or bottles must be labeled prior to administration per sites institutional policy.

7.2.6 Ganitumab Administration

Ganitumab will be administered as an IV infusion every 2 weeks. The IV infusion must be administered via piggyback into a main line of 0.9% NaCl and administered as a continuous IV infusion via controlled infusion. The first dose should be administered over 60 +/- 10 minutes without premedication. If well tolerated, subsequent infusions may be administered over 30 +/- 5 minutes, at the investigators discretion. Infusion times can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion. For patients who are continued on ganitumab after a severe
 infusion reaction of ≥ grade 3, restart infusion at a reduced rate of ≤50% for subsequent cycles.

Before each cycle of protocol treatment, within 48 hours of treatment administration, patients must have:
  - Adequate bone marrow, hepatic, and renal function tests, defined as follows:
    - **Bone Marrow:** WBC ≥ 3000/mm³, ANC ≥ 1000/mm³, platelets ≥ 100,000/mm³
    - **Hepatic:** Total bilirubin < 3.0 mg/dL, AST and ALT ≤ 2.5 x institutional ULN
    - **Renal:** Serum creatinine ≤ 1.5 x institutional ULN.

### 7.2.6.1 Administration via Peripheral IV Access
An experienced and qualified staff member will perform the placement of the peripheral IV access and establishment of a main IV line with 0.9% NaCl. Administration of ganitumab will be piggyback into the main line of 0.9% NaCl if the IV access becomes dislodged and ganitumab extravasates into surrounding tissue the infusion needs to be stopped. The IV must be removed and the site inspected for skin integrity. The subject may develop a reddened area around the site of the infiltration, which is caused by accumulation of ganitumab in the surrounding tissues (depot effect). Remaining ganitumab may be subsequently administered through an alternate IV access following the above guidance.

### 7.2.6.2 Administration via Indwelling Access Device
An indwelling access device will be flushed with a minimum of 5.0 mL of 0.9% NaCl before each infusion of ganitumab to assess patency. Once it is established that the device is patent, a standard IV line using 0.9% NaCl will be attached to the indwelling access device. The administration of ganitumab, diluted in 0.9% NaCl, will be piggybacked into the main line via the use of a controlled infusion pump. Upon completion of the infusion of ganitumab a minimum of 5 ml must be infused into the subject via the main IV line to clear any residual ganitumab from the indwelling access device. Upon disconnection of the IV line from the indwelling access device will be flushed with a minimum of 5.0 mL of 0.9%.

All subjects receiving ganitumab will be carefully monitored throughout and immediately after administration of ganitumab. A physician or medical staff, involved in study evaluations, must be available during the administration of each dose of ganitumab to assess and treat adverse events that may arise during dosing. Subjects will be monitored in the clinic for at least 1 hr after their first dose of ganitumab. Post-dose monitoring may be shortened or discontinued thereafter provided there are no reactions with the first dose.

### 7.2.7 Adverse Events
As of March 2010, reported adverse events among 91 subjects treated with ganitumab monotherapy, in descending order of frequency occurring in at least 10% of subjects were: fatigue, nausea, decreased appetite, thrombocytopenia, pyrexia, anemia, constipation, dyspnea, vomiting, abdominal pain, back pain, peripheral edema, diarrhea, rash, anxiety, cough, chills, arthralgia, depression, hyperglycemia, and pain (including pain in extremities, musculoskeletal pain, and chest pain).

Please refer to the ganitumab investigator brochure (Ed 6.0) for a discussion of adverse effects by individual study.

### 7.2.8 Drug Ordering and Supply
Amgen provides ganitumab free of charge to patients on study. Ganitumab will be distributed by Fisher Clinical Services. No supplies will be shipped to any site until the case has been registered.

The initial drug supply for the induction and concurrent therapy is patient specific. Reorder will be required prior to the maintenance therapy using the reorder form included with the initial shipment which will also be available on the website under protocol specific
regulatory resources. Please follow the instructions on the form. Investigational sites will be supplied with sufficient ganitumab to treat each registered patient as follows:

**Induction and concurrent treatment** shipments (initial patient specific shipments), which will be automatically triggered by patient registration, will contain **10-14** vials of Ganitumab (AMG 479) along with a copy of the A0 indicating the patient case for which the shipment is intended and a form to reorder when the case advances to maintenance therapy.

**Maintenance therapy** drug supply will require reorder using the 1102 reorder form with the option for RUSH overnight delivery. This will result in the receipt of your choice of 4, 6, 8, or **10, 12 or 14** vials of study specific supply of Ganitumab (AMG 479) which is to be pooled and used for any case on maintenance therapy registered at that institution.

Ganitumab (AMG 479) will be shipped from Fisher Clinical Services directly to the institution. Orders will be shipped via one-day shipping on Monday through Wednesday only according to the following schedule:

<table>
<thead>
<tr>
<th>Patient registered with RTOG</th>
<th>Initial e-order transmitted by RTOG</th>
<th>Initial e-order Received by Fisher (by 5PM ET)</th>
<th>Initial Order shipped by Fisher</th>
<th>Initial Order received at site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>Monday</td>
<td>Monday</td>
<td>Tuesday</td>
<td>Wednesday</td>
</tr>
<tr>
<td>Tuesday</td>
<td>Tuesday</td>
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<tr>
<td>Friday</td>
<td>Friday</td>
<td>Friday</td>
<td>Monday</td>
<td>Tuesday</td>
</tr>
</tbody>
</table>

Please take this information into consideration when scheduling initial dosing to assure realistic treatment start dates. Protocol treatment must begin within 7 days of registration.

**All questions regarding drug supply and anticipated delivery dates should be addressed directly to Fisher Clinical Services:**

**FCS Help Desk : 877-253-3080**

This study will be conducted under an IND to be held by RTOG and will require FDA submission and approval as part of the IND. Ganitumab will be supplied to patients on study free of charge.

The Study Agent Shipment Form [SASF; available on the RTOG web site, www.rtog.org under protocol-specific materials/regulatory resources for U.S. sites must be submitted to the CTSU Regulatory Office (Fax 215-569-0266) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution’s first case. The drug supply will not be shipped by Fisher Clinical Services until the patient has been registered. RTOG will notify Fisher Clinical Services to initiate each of these shipments after registration of the patient. Please contact the drug distributor listed in the protocol directly for shipment tracking information and anticipated delivery dates or if a shipment has not been received by the expected date (see Fisher Clinical Help Desk number above).

**Drug Return/Destruction**

All drug should be discarded according to the site’s guidelines, and their disposition should be recorded on the NCI Investigational Agent Accountability Record Form or an accountability form containing the equivalent information at a minimum.
7.2.10 Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines. Separate RTOG accountability forms will be available under the protocol specific regulatory resources tab on the RTOG website for the patient specific induction and concurrent treatment and for the pooled study specific maintenance therapy.

7.3 Gemcitabine (HCl) Agent Information

See package insert for comprehensive information.

7.3.1 Formulation

Gemcitabine is an antineoplastic agent that is structurally related to cytarabine. It is a pyrimidine analogue that is cell-cycle specific. 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.

7.3.2 Mechanism of Action

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.

7.3.3 Preparation

To reconstitute, add 5 mL of 0.9% sodium chloride injection to the 200-mg vial or 25 mL of 0.9% sodium chloride injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL, which includes accounting for the displacement volume of the lyophilized powder.

7.3.4 Administration

The appropriate amount of drug may be administered as prepared or further diluted with 0.9% sodium chloride injection to concentrations as low as 0.1 mg/mL. Each dose will be administered as a 30-minute intravenous infusion.

7.3.5 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 have occurred following therapeutic gemcitabine therapy. Cardiac dysfunction (myocardial infarction, congestive heart failure, and atrial fibrillation) have been infrequently reported.

7.3.6 Storage and Stability

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

7.3.7 Supply

Gemcitabine is commercially available.

7.4 Capecitabine Agent Information

See package insert for comprehensive information.

7.4.1 Formulation

Capecitabine is supplied as a biconvex, oblong film-coated tablet for oral administration. 150 mg AND 500 mg tablets will be utilized in this study. Doses will be
rounded to the nearest 150 mg increment. See Appendix VI for Capecitabine Dosing Table.

7.4.2 Mechanism of Action
Capecitabine is an oral prodrug of 5-fluorouracil. Metabolized in the liver to 5'-deoxy-fluorocytidine, 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.

7.4.3 Preparation
This is an oral agent. 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.

7.4.4 Administration
The capecitabine daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. Dosages will be based on the Dosing Table in Appendix VI. The tablets should be taken with water.

Before each cycle of protocol treatment, within 48 hours of treatment administration, patients must have:
- Adequate bone marrow, hepatic, and renal function tests, defined as follows:
  - Bone Marrow: WBC ≥ 3000/mm³, ANC ≥ 1000/mm³, platelets ≥ 100,000/mm³
  - Hepatic: Total bilirubin ≤ 1.5 x institutional ULN, AST and ALT ≤ 2.5 x institutional ULN
  - Renal: Serum creatinine ≤ 1.5 x institutional ULN.

Patients will be asked to maintain a diary documenting self administration of capecitabine. Prior to starting treatment, the patient will be provided with and instructed in the proper use of a pill diary (see the RTOG 1102 forms listing on the RTOG website) or a calendar to record their daily pill consumption. This record will be checked for compliance by the treating physician. The diary will be retained in the patient’s record for submission to RTOG ONLY upon request; i.e., diaries are not to be submitted but will be retained at the site as source documents. Patients who are non-compliant must be re-instructed in the use of the diary.

7.4.5 Potential Drug Interactions
7.4.5.1 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.

7.4.5.2 Oral Anticoagulants
Altered coagulation parameters and/or bleeding, including death, have been reported in patients receiving capecitabine and coumarin-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.

7.4.5.3 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.

7.4.6 Adverse Events
Common side effects from capecitabine include diarrhea (which may be severe), dermatologic effects (hand-and-foot syndrome referred to as palmar-plantar erythrodysesthesia), 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).

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

7.4.8 Supply
Capecitabine is commercially available.

7.5 Dose Modifications
Dose modifications will be made according to the greatest degree of toxicity. Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) (per Section 7.7).

7.5.1 Dose Modification During Ganitumab and Gemcitabine Pre- and Post-RT
NOTE: See Section 7.5.4 for dose modifications for grade 4 hyperglycemia

7.5.1.1 Hematologic Toxicity
Dose modifications according to blood counts within 48 hours prior to the day of treatment (see the table below):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ganitumab Dose</th>
<th>Gemcitabine Dose</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC ≥ 1,000 cells/μl and platelets ≥ 100,000</td>
<td>12 mg/kg</td>
<td>1,000 mg/m²</td>
<td>No dose modification; full dose of ganitumab and gemcitabine</td>
</tr>
<tr>
<td>ANC 750 – &lt; 1,000 and/or platelets 50,000 – &lt;100,000 cells/μl</td>
<td>12 mg/kg</td>
<td>750 mg/m²</td>
<td>Treat at reduced dose. Dose reduction is not permanent, unless the patient also has a grade 3 or 4 non-hematologic toxicity related to treatment, if not, when ANC ≥ 1,000 cells/μl and platelets ≥ 100,000 cells/μl resume full-dose gemcitabine</td>
</tr>
<tr>
<td>ANC 500 – &lt; 750 cells/μl persisting for &lt; 7 days and platelets ≥ 50,000</td>
<td>12mg/kg</td>
<td>Hold</td>
<td>When ANC ≥ 1,000 cells/μl and platelets ≥ 100,000 cells/μl, resume at current dose level of gemcitabine</td>
</tr>
<tr>
<td>ANC 500 – &lt; 750 cells/μl that persists for more than 7 days</td>
<td>Hold</td>
<td>Hold</td>
<td>When ANC ≥ 1,000 cells/μl and platelets ≥ 100,000 cells/μl, resume at current dose level of gemcitabine and ganitumab</td>
</tr>
<tr>
<td>ANC 500 – &lt; 750 cells/μl and/or platelets 25,000 – &lt; 50,000 cells/μl (without grade 2 bleeding)</td>
<td>Hold</td>
<td>Hold</td>
<td>When ANC ≥ 1,000 cells/μl and platelets ≥ 100,000 cells/μl, resume at permanent 25% dose level of gemcitabine and full dose of ganitumab</td>
</tr>
</tbody>
</table>
ANC <500 cells/µl and/or platelets <25,000 cells/µl

Hold

Hold

When ANC ≥ 1,000 cells/µl and platelets ≥ 100,000 cells/µl, 50% dose reduction of ganitumab and gemcitabine at 25% dose reduction. This dose reduction for gemcitabine is permanent for induction and post RT gemcitabine and ganitumab.

2<sup>nd</sup> occurrence of grade 4 neutropenia and/or thrombocytopenia AE

Discontinue

Hold

Discontinuation of ganitumab for induction and post RT treatment when ANC ≥ 1,000 cells/µl and platelets ≥ 100,000 cells/µl, resume gemcitabine at second 25% dose reduction. This dose reduction for gemcitabine is permanent for induction and post RT gemcitabine.

3<sup>rd</sup> occurrence of grade 4 hematologic AE

Discontinue

Hold

Third 25% dose reduction. This dose reduction for gemcitabine is permanent for induction and post RT gemcitabine.

4<sup>th</sup> occurrence of grade 4 hematologic AE

Discontinue

Discontinue

Discontinue

Additional Notes:

- Ganitumab and gemcitabine will be discontinued for grade 4 neutropenia or thrombocytopenia persisting more than 28 days.
- Patients who have grade 3 or greater thrombocytopenia with grade 2 or greater bleeding will have ganitumab permanently discontinued during gemcitabine.
- Any permanent dose reduction of gemcitabine that occurs during induction treatment will apply to post-RT gemcitabine. Dose reductions of ganitumab from hematologic toxicity during when ganitumab is combined with gemcitabine do not apply to ganitumab administered with capecitabine during radiation.

7.5.1.2 Non-Hematologic Toxicity (REFER TO Section 7.5.4 FOR DOSE MODIFICATIONS FOR HYPERGLYCEMIA)

Dose Modification for Non-Hematologic Toxicity/Induction and Post-RT ganitumab and Gemcitabine Related to Treatment and Deemed To Be Clinically Significant

<table>
<thead>
<tr>
<th>Grade 3 or 4 Non-Hematologic Toxicity</th>
<th>Ganitumab Dose</th>
<th>Gemcitabine Dose</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Occurrence</td>
<td>HOLD</td>
<td>HOLD</td>
<td>Resume when toxicity has resolved to ≤</td>
</tr>
<tr>
<td>Occurrence</td>
<td>Action 1</td>
<td>Action 2</td>
<td>Action 3</td>
</tr>
<tr>
<td>------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Occurrence</td>
<td>HOLD</td>
<td>HOLD</td>
<td>Resume when toxicity has resolved to ≤ grade 2 at a second 25% reduction of gemcitabine and full-dose ganitumab 12mg/kg. The dose reduction to gemcitabine is permanent.</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Occurrence</td>
<td>HOLD</td>
<td>HOLD</td>
<td>Resume when toxicity has resolved to ≤ grade 2 at a third 25% reduction of gemcitabine and full-dose ganitumab 12mg/kg. The dose reduction to gemcitabine is permanent.</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; Occurrence</td>
<td>Discontinue</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

For patients who are continued on ganitumab after an infusion reaction ≥ grade 3, restart infusion at a reduced rate of ≤ 50% for subsequent cycles.

Ganitumab and gemcitabine will be discontinued for grade 3 and 4 toxicity that persists > 28 days.

If the start of a cycle is delayed due to grade 3 or 4 gemcitabine-related toxicity or grade 3 or 4 non-hematologic toxicity, then ganitumab should also be delayed until the patient has recovered.

Patients with adverse events not related to treatment, such as cholangitis from blocked biliary stents or infection do not require dose reductions when treatment is resumed (after recovery from these adverse events to ≤ grade 2).

Subjects requiring initiation of therapeutic anti-coagulation treatment while on study treatment (e.g., for deep venous thrombosis or asymptomatic pulmonary embolism) will have ganitumab withheld until the therapeutic anti-coagulation treatment is stable (e.g., on coumadin with an INR of 2 to 3 for at least 7 days). Subjects who remain on full dose low molecular heparin (without Coumadin) as therapeutic anti-coagulation may restart ganitumab at the discretion of the investigator.

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

Subjects with a symptomatic PE occurring during treatment will permanently discontinue ganitumab.
Ganitumab must be permanently discontinued if a subject experiences a grade 4 infusion reaction.

**7.5.2** Ganitumab: Additional Guidelines During Ganitumab and Gemcitabine

**7.5.2.1** Infusion reactions

Premedication is not required for routine infusions. If during or after any infusion, a reaction occurs, premedication with diphenhydramine may be utilized. Infusion times can be extended to a maximum of 120 minutes. Infusions will be stopped for patients who experience any serious infusion reaction (eg, dyspnea, chest tightness, fever, rigors or hypertension). Continuation of dosing will be based on the severity and resolution of the event and will be at the discretion of the investigator. At the discretion of the investigator, treatment of an infusion reaction may include Solu-Medrol, ranitidine, diphenhydramine; premedications (dexamethasone or Solu-Medrol, ranitidine, diphenhydramine or equivalents) may be considered for future infusions. Suspected infusion reactions should be reported as an adverse event. For patients who are continued on ganitumab after an infusion reaction ≥ grade 3, restart infusion at a reduced rate of ≤ 50% for subsequent cycles.

**7.5.2.2** Extravasation

If ganitumab extravasates during IV administration, the infusions must be stopped immediately. The patient may develop a reddened area around the site of the infiltration. The IV must be removed. Any remaining ganitumab may be subsequently administered through an alternate IV access.

**7.5.3** Dose Modifications During Concurrent Ganitumab/Capecitabine/RT

*NOTE: See Section 7.5.4 for dose modifications for grade 3 and grade 4 hyperglycemia*

**7.5.3.1** Hematologic Toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ganitumab</th>
<th>Capecitabine</th>
<th>3D-CRT</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC ≥ 1000 cells/µl and platelets &gt; 75,000 cells/µl</td>
<td>Full dose at assigned level</td>
<td>Full dose at assigned level</td>
<td>Continue</td>
<td>No dose modification RT continues</td>
</tr>
<tr>
<td>ANC 750–999 cells/µl lasting ≤ 7 days and/or platelets 50,000–75,000 cells/µl</td>
<td>Full dose at assigned level</td>
<td>HOLD</td>
<td>Continue</td>
<td>When ANC &gt; 1000 cells/µl and platelets &gt; 75,000 cells/µl, resume capecitabine at <strong>permanent</strong> 25% dose reduction. RT continues</td>
</tr>
<tr>
<td>ANC 500–999 cells/µl lasting &gt; 7 days</td>
<td>HOLD</td>
<td>HOLD</td>
<td>Continue</td>
<td>When ANC &gt; 1000 cells/µl and platelets &gt; 75,000 cells/µl, resume full dose ganitumab and <strong>permanent</strong> 25% dose reduction of capecitabine. RT continues</td>
</tr>
<tr>
<td>ANC 500 – &lt;750 cells/µl and/or platelets 25,000 – &lt;50,000 cells/µl (without grade 2 bleeding)</td>
<td>HOLD</td>
<td>HOLD</td>
<td>Continue</td>
<td>When ANC ≥ 1,000 cells/µl and platelets ≥ 100,000 cells/µl, resume at 25% dose reduction of capecitabine and full dose of ganitumab.</td>
</tr>
<tr>
<td>First episode: ANC &lt;500 cells/µl and/or platelets</td>
<td>HOLD</td>
<td>HOLD</td>
<td>HOLD</td>
<td>When ANC &gt; 1000 cells/µl and platelets ≥ 50,000 cells/µl, resume</td>
</tr>
</tbody>
</table>
<25,000 cells/µl

at 50% dose reduction of ganitumab at assigned level and permanent reduction 25% of capecitabine. XRT may resume when ANC ≥ 500 cells/µl and platelets ≥ 50,000 cells/µl.

Second episode: ANC <500 cells/µl and/or platelets <25,000 cells/µl

DISCONTINUE HOLD HOLD When ANC > 1000 cells/µl and platelets ≥ 50,000 cells/µl, discontinue protocol treatment with ganitumab and permanent reduction 25% of capecitabine. XRT may resume when ANC ≥ 500 cells/µl and platelets ≥ 50,000 cells/µl.

Additional Notes:
- Patients who have required 2 dose reductions and who experience a third episode of ANC < 1000 cells/µl and platelets < 75,000 cells/µl will complete 3D-CRT but will not receive any additional ganitumab or capecitabine.
- Grade 3 or greater thrombocytopenia with grade 2 or greater bleeding would lead to discontinuation of ganitumab.
- Ganitumab and gemcitabine will be discontinued for grade 4 neutropenia or thrombocytopenia persisting more than 28 days.

7.5.3.2 Non-Hematologic Toxicity
Patients with adverse events not related to treatment, such as cholangitis from blocked biliary stents or pulmonary embolus from hypercoagulable state, after recovery from these adverse events, on resumption of treatment, do not require dose reductions when treatment is resumed.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ganitumab</th>
<th>Capecitabine</th>
<th>3D-CRT</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 AE, (clinically significant) 1st Occurrence</td>
<td>HOLD</td>
<td>HOLD</td>
<td>HOLD</td>
<td>When resolved to ≤ grade 2, then resume at full-dose ganitumab at assigned level and <strong>permanent 25%</strong> dose reduction of capecitabine; RESUME RT</td>
</tr>
<tr>
<td>Grade 3 or 4 AE, (clinically significant) 2nd Occurrence</td>
<td>HOLD</td>
<td>HOLD</td>
<td>HOLD</td>
<td>When resolved to ≤ grade 2, then resume full-dose ganitumab at assigned level and a <strong>second permanent 25%</strong> dose reduction of capecitabine</td>
</tr>
</tbody>
</table>
Grade 3 or 4 AE, (clinically significant) 3rd Occurrence

| Hold for 28 days | Hold for 28 days | Hold for 28 days | When resolved to ≤ grade 2, then resume full-dose ganitumab at assigned level and a third permanent 25% dose reduction of capecitabine |
---|---|---|---|

Grade 3 or 4 AE, (clinically significant) 4th Occurrence

| Discontinue | Discontinue | Hold for 28 days | Discontinue |
---|---|---|---|

Any grade 3 or 4 AE that persists for > 28 days

| Discontinue | Discontinue | Hold for 28 days | Discontinue |
---|---|---|---|

Grade 2 hand/foot syndrome

| Continue full-dose ganitumab at assigned dose level | Hold for 28 days | RT continues | When resolved to ≤ grade 1, then resume assigned level of capecitabine at 25% dose reduction |
---|---|---|---|

Grade 3 hand/foot syndrome

| Hold full-dose ganitumab at assigned dose level | Hold for 28 days | Hold for 28 days | When resolved to ≤ grade 1, then resume assigned level of capecitabine at 50% dose reduction and ganitumab at full dose. |
---|---|---|---|

Patient will be removed from protocol treatment and not receive additional ganitumab if unable to receive radiation for > 28 days due to hematologic or nonhematologic toxicity. For patients who are continued on ganitumab after an infusion reaction of ≥ grade 3, restart infusion at a reduced rate of ≤ 50% for subsequent cycles.

7.5.4 Dose Modifications for Grade 3 and Grade 4 Hyperglycemia (Induction, Concurrent, and Maintenance Phases)

- Grade 3 and grade 4 Hyperglycemia deemed related to ganitumab will managed per local institutional guidelines and ganitumab will be withheld until hyperglycemia resolves to ≤ grade 1.
- Patients who develop a first episode of grade 4 hyperglycemia related to ganitumab will have a 50% dose reduction of ganitumab when hyperglycemia resolves to ≤ grade 1. Dosages of gemcitabine and capecitabine do not require reduction for hyperglycemia.
- Patients who develop 2 or more instances of grade 4 hyperglycemia related to ganitumab will have ganitumab permanently discontinued.
- In patients who develop diabetic ketoacidosis or hyperosmolar state, ganitumab will be permanently discontinued.

7.5.5 Hearing Loss

Audiograms should be considered for subjects complaining of hearing loss. Any history of hearing loss should be documented at baseline. NOTE: patients with grade 2 or worse hearing loss at the time of study entry will not be eligible. Hearing loss will be managed according to other non-heme toxicity.

7.6 Modality Review

The Medical Oncology Co-Chairs, Howard Safran, MD, and Naimish Pandya, MD, will perform a Chemotherapy Assurance 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, Not Per Protocol, and Not Evaluable.
All reviews will be completed prior to escalating to the next dose level or making an MTD determination.

7.7 Adverse Events

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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 website (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. SAEs can also be accessed through the RTOG website (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.7.1 Adverse Events (AEs)

**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: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

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 on the AE section of the appropriate case report form (see Section 12.1).

**Note**: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.8 also must be reported via AdEERS.

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will 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 via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies**: All unexpected potentially related SAEs
- **Phase I Studies**: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship

**Definition of an SAE**: Any adverse experience occurring during any part of protocol treatment and 30 days after 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, 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. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the 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. The RTOG Case Number without any leading zeros should be used 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 select the option in AdEERS to send a copy of the report to the FDA or 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 via the AdEERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

7.8 AdEERS Expedited Reporting Requirements
CTEP defines expedited AE reporting requirements for phase 1 trials as described in the table below. Important: All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention
FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 and Grade 2 Timeframes</th>
<th>Grade 3-5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
</tr>
<tr>
<td>≥ 24 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization</td>
<td>Not required</td>
<td></td>
</tr>
<tr>
<td>≥ 24 hrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE**: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

**Expedited AE reporting timelines are defined as:**

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

1 Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

- **Expedited 24-hour notification followed by complete report within 5 calendar days for:**
  - All Grade 3, 4, and Grade 5 AEs

- **Expedited 10 calendar day reports for:**
  - Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

2 For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

**NOTE**: Deaths clearly due to progressive disease should **NOT** be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a non-CTEP-IND:**
None
8.0 SURGERY

8.1 Surgical Quality Assurance Reviews
In patients with a marked response to treatment, surgery may be attempted based on the discretion of the attending surgeon. Chemotherapy, ganitumab and RT should be stopped at least 4 weeks prior to attempted surgery and not restarted until at least 4 weeks after surgery. Patients must restart protocol treatment no longer than 8 weeks after surgery or the case will be considered a treatment deviation.

Operative reports for patients on study who are taken for exploration and consideration of resection will be examined. The reasons that patients are found to be resectable or not will be evaluated and recorded.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

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 in the institution’s source documentation.

9.1.1 Prophylaxis for Gastric Ulceration During Chemoradiation
It is recommended that patients be on a proton pump inhibitor during and for 1 month after radiation. If any new epigastric pain develops, ulceration should be expected and sucralfate should be started. Upper endoscopy may be performed as clinically directed.

9.1.2 Anticoagulants: Caution Concerning Co-Administration of Warfarin and Capecitabine
A significant interaction occurs with co-administration of capecitabine and warfarin that can result in severe prolongation of the prothrombin time and resultant increased risk of severe bleeding. Patients requiring warfarin should have their prothrombin time monitored carefully according to institutional guidelines. Low molecular weight heparin does not interact with warfarin or capecitabine and is the preferred agent for patients requiring anticoagulation.

9.1.3 Hematopoietic Growth Factors
9.1.3.1 Erythropoietin is allowed.
9.1.3.2 Myeloid growth factors may be utilized to treat CTCAE grade 3-4 ANC.

9.1.4 Management of Grade 4 Hyperglycemia
Oral hypoglycemics or regular insulin should be instituted per Section 7.5.4.

9.2 Non-Permitted Supportive Therapy
9.2.1 Other investigational chemotherapy agents
9.2.2 Other chemotherapeutic agents
9.2.3 Other monoclonal antibody
9.2.4 Sorivudine or brivudine A
9.2.5 Cimetidine
9.2.6 G-CSF agents on the days the patient is receiving treatment

10.0 TISSUE/SPECIMEN SUBMISSION
NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.

If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient’s specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission
The RTOG Biospecimen Resource at the University of California San Francisco 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 Biospecimen Resource 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 Biospecimen Resource also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue, plasma, and whole blood will be submitted to the RTOG Biospecimen Resource for the purpose of banking (highly recommended).

10.2 Specimen Collection for Tissue Banking (optional but highly recommended)
For patients who have consented to participate in the tissue/blood component of the study (See Appendix I).

10.2.1 Tissue
The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1.1 One H&E stained slide
10.2.1.2 A paraffin-embedded tissue block of the tumor (preferred) or 10 five micron unstained sections cut onto positive charged slides labeled with the surgical pathology number. Block or slides must all be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

NOTE: If surgery is done after treatment an optional H&E and block should also be submitted.

10.2.1.3 A Pathology Report documenting that the submitted block or slides contains 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.

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

10.2.2 Plasma and Whole Blood: for detailed instruction on collection and shipping see Appendix VII.

10.2.2.1 Plasma Collection Schedule
Plasma will be collected at the following 3 time points:
- Pretreatment,
- Following induction chemotherapy but before start of chemoradiation, and
- 21-42 days following completion of chemoradiation.

10.2.2.2 Whole Blood Collection Schedule
Whole blood for DNA will be collection once during pretreatment. (Note if the site missed this collection time point, the site may collect whole blood at any time point or follow-up visit.)

10.2.2.3 The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the biospecimen; the RTOG protocol number; the patient’s case number; and method of storage, for example, stored at -80° C, must be included.

10.3 Storage Conditions
Store at -80° C (-70° C to -90° C) until ready to ship. If a -80° C Freezer is not available:
- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only).
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).
Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

### 10.4 Specimen Collection Summary

**Specimens for Tissue Banking** *(optional but highly recommended)*

<table>
<thead>
<tr>
<th>Specimens taken from patient:</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative H&amp;E stained slides of the primary tumor</td>
<td>Once: Pretreatment only</td>
<td>H&amp;E stained slide Pre-treatment</td>
<td>Slide shipped ambient</td>
</tr>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or 10 five micron unstained sections on positive charged slides</td>
<td>Once: Pretreatment only</td>
<td>Paraffin-embedded tissue block, or 10 five micron unstained sections cut onto positively charged will be permitted ONLY for sites that cannot submit a block</td>
<td>Block or slides shipped ambient</td>
</tr>
<tr>
<td>Plasma: 5-10 mL of whole blood in EDTA tube #1 (purple/lavender top) and centrifuge</td>
<td>3 times: 1) Pretreatment; 2) Following induction chemotherapy but before start of chemoradiation; 3) 2 months following completion of chemoradiation</td>
<td>Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (5 to 10)</td>
<td>Plasma sent frozen on dry ice via overnight carrier (Mon-Wed)</td>
</tr>
<tr>
<td>DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix</td>
<td>Pre-treatment. (Note if site missed this collection time point site may collect whole blood at any time point or follow-up visit).</td>
<td>Frozen whole blood samples containing 1 ml per aliquot in 1 ml cryovials (3 to 5)</td>
<td>Whole blood sent frozen on dry ice via overnight carrier (Mon-Wed)</td>
</tr>
<tr>
<td>Surgical Specimens:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representative H&amp;E stained slides of the surgical specimen from the primary tumor after treatment</td>
<td>Post-treatment</td>
<td>H&amp;E stained slide Post-treatment</td>
<td>Slide shipped ambient</td>
</tr>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor taken after treatment</td>
<td>Post-treatment</td>
<td>Paraffin-embedded tissue block</td>
<td>Block shipped ambient</td>
</tr>
</tbody>
</table>

### 10.5 Submit materials for Banking as follows:

**U. S. Postal Service Mailing Address:** For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco Campus Box 1800
2340 Sutter St, Room S341
San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.):** For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter St, Room S341
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu
10.6 Reimbursement
RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/LinkClick.aspx?fileticket=Csxz1v1hEk%3d&tabid=323). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.7 Confidentiality/Storage

10.7.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource 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.

10.7.2 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: See Appendix II.

11.2 Evaluation During Treatment
11.2.1 In all clinic visits and weekly during each cycle, sites will question patients regarding compliance with study instructions.

11.3 Measurement of Response

CT imaging with IV contrast using 5 mm maximum slice thickness is recommended for all evaluation of the primary tumor. If MRI is used, comparable scanners and imaging techniques should be used in all scans.

- **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 by chest X-ray, ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

- **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Response Criteria: Evaluation of Target Lesions

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

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

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

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

11.4 Criteria for Discontinuation of Protocol Treatment

Protocol treatment may be discontinued for any of the following reasons:
- Progression of disease;
- Adverse events, as described in Section 6.0 and 7.0;
- Delays in protocol treatment > 4 weeks.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

Data should be submitted to:
RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

*If a data form is available for web entry, it must be submitted electronically.

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

<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>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Surgical pathology report (S5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Operative Report (S2) (If applicable)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>CT/MRI Report of Abdomen /pelvis (C3)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Surgery Form (S1) (required for all patients who undergo exploration and consideration of resection)</td>
<td>2 weeks after surgical exploration for consideration of resection during protocol treatment</td>
</tr>
</tbody>
</table>
Surgical pathology Report (S5) (If applicable)

Supplementary Followup (FS)  
Prior to start of concurrent treatment but after post induction CT and at 4 weeks post RT completion

Induction Treatment Form (FO)  
1 week after EACH induction treatment completed

Concurrent Treatment From (TF)  
1 week after concurrent treatment completed

Maintenance Treatment Form(SF)  
1 week after each maintenance 28 day cycle

Follow-up Form (F1)  
Q3 months from the start of maintenance treatment X 2 years; Q4 months X 1 year; then annually; source documentation is required for any reported tumor event

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information (DD)</td>
<td></td>
</tr>
<tr>
<td>Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist</td>
<td>Submit for RT plan review and approval at least 14 days PRIOR to RT start</td>
</tr>
<tr>
<td>Digital data submission includes the following:</td>
<td></td>
</tr>
<tr>
<td>• CT data, critical normal structures, all GTV, CTV, and PTV contours</td>
<td></td>
</tr>
<tr>
<td>• Digital beam geometry for initial and boost beam sets</td>
<td></td>
</tr>
<tr>
<td>• Doses for initial and boost sets of concurrently treated beams</td>
<td></td>
</tr>
<tr>
<td>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)</td>
<td></td>
</tr>
<tr>
<td>Digital Data Submission Information Form (DDSI) – Submitted online (Form located on ATC web site, <a href="http://atc.wustl.edu/forms/DDSI/ddsi.html">http://atc.wustl.edu/forms/DDSI/ddsi.html</a>)</td>
<td></td>
</tr>
<tr>
<td>Hard copy isodose distributions for total dose plan (T6)</td>
<td></td>
</tr>
<tr>
<td>MRI/CT with contrast fused with planning CT (see Appendix V for details)</td>
<td></td>
</tr>
<tr>
<td>NOTE: Sites must notify ITC via e-mail (<a href="mailto:itc@wustl.edu">itc@wustl.edu</a>) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information Radiotherapy Form (T1) [copy to HQ and ITC]</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Daily Treatment Record (T5) [copy to HQ and ITC]</td>
<td></td>
</tr>
<tr>
<td>Modified digital patient data as required through</td>
<td></td>
</tr>
</tbody>
</table>
consultation with Image-Guided Therapy QA Center

12.2.1 Digital Data Submission to ITC

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint
Dose limiting toxicity for ganitumab and capecitabine given concurrently with radiation therapy.

13.1.2 Secondary Endpoints
13.1.2.1 Adverse events at any time
13.1.2.2 Response rate (for patients treated at maximum tolerated dose of ganitumab)
13.1.2.3 Overall survival (for patients treated at maximum tolerated dose of ganitumab)

13.2 Sample Size

13.2.1 Evaluation of Adverse Events for MTD
Adverse events will be scored according to the NCI CTCAE version 4 criteria. Dose limiting toxicity (DLT) is defined as any of the following occurring during chemoradiation or within 21 days from the completion of chemoradiation and being reported as probably or definitely related to treatment:

- Grade 4 non-hematologic toxicity
- Grade 4 Febrile neutropenia
- Grade 4 thrombocytopenia or neutropenia toxicity lasting > 7 days;
- Grade 3 non-hematologic toxicity, preventing treatment for > 7 days;
- Elevation of ALT or AST > 10 x upper limit of normal for > 7 days (and not due to blocked stent or disease progression) also will be considered a DLT;
- Any Grade 5 AE.

13.2.2 Dose Escalation
The following tables show the potential dose levels of ganitumab and capecitabine to be given concurrently with RT in this study:

<table>
<thead>
<tr>
<th>Table A</th>
<th>Ganitumab (mg/kg days 1, 15, 29)</th>
<th>Capecitabine (mg/m² BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level -1a</td>
<td>6</td>
<td>825</td>
</tr>
<tr>
<td>Dose Level 1a</td>
<td>12</td>
<td>825</td>
</tr>
<tr>
<td>Dose Level 2a</td>
<td>20</td>
<td>825</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table B (if needed)</th>
<th>Ganitumab (mg/kg days 1, 15, 29)</th>
<th>Capecitabine (mg/m² BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level -1b</td>
<td>6</td>
<td>625</td>
</tr>
</tbody>
</table>
Evaluable patients will be defined as any eligible patient who begins concurrent radiation therapy and systemic treatment. The potential dose escalation/de-escalation pathways are shown in Table C below. The first group of patients will be entered onto Dose Level 1a. For a given dose level assessment, after 6 evaluable patients have been followed for a minimum of 21 days from the completion of concurrent radiation therapy and systemic treatment, if there are 0 or 1 DLT (as defined in Section 13.2.1), the dose level will be judged to be acceptable. If a dose level is acceptable and it is the final dose level on the escalation/de-escalation path, it will be determined to be the MTD. If a dose level is acceptable and there are additional escalations, then patients will begin to be accrued at the next higher dose level. If a dose level is not acceptable (2 or more DLTs) and it is the final dose level on the escalation/de-escalation path, the last acceptable dose level will be determined to be the MTD. If a dose level is not acceptable and there are additional de-escalations, then patients will begin to be accrued at the next lower dose level. If at any time a grade 5 treatment-related adverse event is observed, it will be reviewed by the study chairs. After the required number of evaluable patients have been accrued for a given dose level, the accrual will be temporarily suspended while the safety of that dose level is assessed.

### Table C:
RTOG 1102 Dose Escalation/De-escalation Paths

<table>
<thead>
<tr>
<th>Starting Dose Level</th>
<th>Possible Dose Escalation/De-escalation Paths</th>
<th>Last Dose Level Assessed</th>
<th>MTD Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a up to 2a</td>
<td></td>
<td>2a</td>
<td>2a</td>
</tr>
<tr>
<td>1a up to 2a</td>
<td>→ down to 2b</td>
<td>2b</td>
<td>2b</td>
</tr>
<tr>
<td>1a up to 2a</td>
<td>→ down to 2b</td>
<td>2b</td>
<td>1a</td>
</tr>
<tr>
<td>1a down to 1b</td>
<td></td>
<td>1b</td>
<td>1b</td>
</tr>
<tr>
<td>1a down to 1b</td>
<td>→ down to -1a</td>
<td>-1a</td>
<td>-1a</td>
</tr>
<tr>
<td>1a down to 1b</td>
<td>→ down to -1a</td>
<td>-1b</td>
<td>-1b</td>
</tr>
<tr>
<td>1a down to 1b</td>
<td>→ down to -1a</td>
<td>-1b</td>
<td>none</td>
</tr>
</tbody>
</table>

The number of evaluable patients that will be needed for the phase I portion of this study depends on the number of dose escalations/de-escalations. The minimum and maximum number of dose levels to be assessed to determine the MTD are 2 and 4 respectively. Assuming no more than 2 patients per dose level are found to be ineligible or did not start protocol treatment, the maximum number of patients accrued to determine the MTD will be 32.

Once the MTD is determined, an expanded cohort of 10 additional patients will be accrued at the MTD to further evaluate AEs.

### 13.2.3 Patient Accrual
Allowing time for institutions to get this protocol through their IRB and be approved through the credentialing process, accrual will begin approximately 3-6 months from the date of the study is initially broadcast to RTOG members. Based on prior RTOG unresectable pancreas trials (RTOG 9812, 0020, and 0411), patient accrual is projected to be 8 patients per month. Accrual and evaluation of a given dose level will take approximately 3.5 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 Analysis Plan
#### 13.3.1 Interim Reporting
Interim reports with statistical analyses are prepared every six months until the primary endpoint results have been presented. In general, the interim reports will contain information about:

- 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 adverse events due to protocol therapy

13.3.2 Data Safety Monitoring Board (DSMB) Review

To monitor the safety of this study, the RTOG DSMB will officially review this study twice per year in conjunction with the RTOG semi-annual meeting and on an “as needed” basis in between meetings.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.3.3 Analysis for Reporting the Initial Treatment Results

13.3.3.1 Reporting of the MTD

This analysis will be undertaken for each treatment regimen when the MTD has been established. The usual components of the analysis are:

- tabulation of all cases entered and reasons for any patients excluded from the analysis
- institutional accrual
- patient accrual rate
- distribution of important pretreatment characteristics
- compliance rates of treatment delivery with respect to the protocol prescription
- observed results with respect to the appropriate endpoints described in Section 13.1.1.

13.3.3.2 Efficacy Endpoints

This analysis will be limited to the patients treated at the MTD, including the expanded cohort of 10 patients, and will be done when these patients have potentially been followed for 1 year. Overall survival will be estimated with the Kaplan-Meier method (Kaplan 1958).

13.4 Gender and Minorities

### Projected Distribution of Gender and Minorities

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>15</td>
<td>22</td>
<td>37</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
<td>17</td>
<td>25</td>
<td>42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>14</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>17</td>
<td>25</td>
<td>42</td>
</tr>
</tbody>
</table>
REFERENCES


Hadsell DL, Bonnette SG, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: A randomized phase II study of conatumumab (C) or AMG 479 (A) or placebo (P) plus gemcitabine (G) in patients (pts) with metastatic pancreatic cancer (mPC). J Clin Oncol. 2010;28(suppl):15s, abstract 4035.


Lu J, Deng H, Tang, R et al. Exposure-response (E-R) analysis to facilitate phase III (P3) dose selection for ganitumab (GAN, AMG 479) in combination with gemcitabine (G) to treat metastatic pancreatic cancer (mPC). *J Clin Oncol* 2011; 29: (suppl; abstr 4049)


APPENDIX I

RTOG 1102

Informed Consent Template for Cancer Treatment Trials (English Language)

A Phase I Study of Induction Ganitumab and Gemcitabine, Followed by Ganitumab, Capecitabine, and 3D-Conformal Radiation Therapy (3D-CRT) With Subsequent Maintenance Therapy 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, which means your pancreatic cancer cannot be removed by surgery but has not spread to other organs.

Why is this study being done?
The purpose of this study is to test the safety of the drug ganitumab when combined with standard chemotherapy and radiation for patients with locally advanced (non-resectable) pancreatic cancer. If the combination is found to be safe, future studies may test whether ganitumab plus standard therapy is useful against cancer.

Gemcitabine, capecitabine, and radiation are standard treatments for locally advanced pancreatic cancer. Gemcitabine is an intravenous chemotherapy drug and capecitabine is a type of chemotherapy pill. Ganitumab is an investigational drug, which means it is not approved by the Food and Drug Administration (FDA). Ganitumab is an antibody, which means it is a protein that can attach to a very specific part of a cell. In the test tube, ganitumab has activity against pancreatic cancer cells. Ganitumab has been tested without radiation in patients with metastatic pancreatic cancer.

How many people will take part in the study?
Between 6 and 42 patients will be treated on this study.

What will happen if I take part in this research study?
The dose of ganitumab that you receive with capecitabine and radiation depends on when you take part in the study. Patients will be treated in groups of 6 patients. Only after 6 patients have completed treatment at a dose level, and the dose level is determined to be safe, will 6 more patients start a higher dose level of ganitumab. Your study doctor will tell you what dose level of ganitumab you are receiving. If too many side effects were seen in the first 6 patients, then the dose of capecitabine will be reduced to a dose that is lower than the standard dose. Once the best dose level of
ganitumab and capecitabine is found, approximately 10 patients will be treated at that dose level.

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.

- Biopsy
- History and physical exam
- Blood tests
- Abdominal/pelvic CT/MRI scan
- Chest CT or whole body PET/CT

During the study:

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 during study treatment. They are part of regular cancer care.

- Physical exam: Monthly during ganitumab and gemcitabine treatment, then weekly during radiation treatment, and then at least monthly
- Blood tests: Weekly
- Abdominal CT/MRI: Prior to starting radiation, then every 3 months while you are receiving protocol treatment.
- Chest CT or whole body PET/CT: Prior to starting radiation, then every 3 months while you are receiving protocol treatment.

You will receive 2 months of chemotherapy followed by radiation therapy and chemotherapy at the same time, followed by more chemotherapy as long as the tumor does not grow or spread. For the first 2 months, gemcitabine will be administered intravenously once per week for 3 weeks on and 1 week off and ganitumab will be administered intravenously every 2 weeks. Following that, radiation will be given daily for 28 treatments Monday through Friday, together with an oral chemotherapy (pill) called capecitabine. Ganitumab will also be given intravenously during radiation every 2 weeks. After radiation, treatment will continue with gemcitabine weekly for 3 weeks on and 1 week off and ganitumab every 2 weeks as long as the tumor does not grow or spread.

You will be asked to complete a pill diary to help document the amount of capecitabine that you take and when you take it. You will fill out the pill diary each time you take capecitabine; you will write the date and number of pills each time you take them in the morning and the evening. You will bring the pill diary with you to each weekly visit with your study doctor. The study doctor will keep the completed pill diary in your chart when you have finished treatment.
Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

<table>
<thead>
<tr>
<th>Start Here</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
</tr>
<tr>
<td>Diagnosis of Locally Advanced Pancreatic Cancer</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td><strong>Pre-Radiation Chemotherapy Treatment for 2 months</strong></td>
</tr>
<tr>
<td>- Gemcitabine intravenously once/week for 3 weeks on, 1 week off,</td>
</tr>
<tr>
<td>- Ganitumab intravenously every 2 weeks</td>
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<tr>
<td>↓</td>
</tr>
<tr>
<td><strong>Chemotherapy Plus Radiation Treatment for 5 ½ Weeks (28 radiation treatments)</strong></td>
</tr>
<tr>
<td>- Radiation Monday-Friday</td>
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<tr>
<td>- Capecitabine orally every day</td>
</tr>
<tr>
<td>- Ganitumab intravenously every 2 weeks</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td><strong>Post-Radiation Chemotherapy Treatment for as Long as Tumor Does Not Grow or Spread</strong></td>
</tr>
<tr>
<td>- Gemcitabine intravenously once/week for 3 weeks on, 1 week off</td>
</tr>
<tr>
<td>- Ganitumab intravenously every 2 weeks</td>
</tr>
</tbody>
</table>

When you are finished with study treatment you will have the following exams, tests, and procedures that are part of standard cancer care.

- Physical exam: Every 3 months for the first 2 years after the end of radiation treatment, every 4 months for the next year, then annually
- Abdominal CT/MRI: Every 3 months after the end of radiation until your disease grows or spreads
- Chest CT or whole body PET/CT: Every 3 months for the first 2 years after the end of radiation treatment, every 4 months for the next year, then annually

How long will I be in the study?

You will be on the study treatment for as long as your cancer does not grow and you do not have severe side effects. Once you have finished the study treatment, we would like to keep track of your medical condition for the rest of your life to look at the long-term effects of the study treatment.
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 him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up 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? (4/23/12)

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers 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 radiation or stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away.

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 ganitumab

As of March 24, 2011 approximately 902 subjects have received ganitumab in research studies.

Because the subjects who have received ganitumab are patients with cancer who have side effects related to their disease, not all side effects that subjects have experienced are considered caused by ganitumab. The physicians treating these subjects were asked to use their judgment in deciding whether the side effects were caused by ganitumab.

Subjects in clinical studies using ganitumab have reported the following side effects that are possibly related to ganitumab.

Very Likely
- Feeling tired
- Chills
- Low platelet count (which can increase the risk of bleeding)
- Nausea
- Diarrhea
Likely
- Fever
- Rash
- Skin lesion, including dry skin, redness of skin and red spots
- Vomiting
- Decreased appetite
- Decreased weight
- Constipation
- Decreased number of red blood cells (which can decrease delivery of oxygen throughout the body and cause fatigue)
- Decreased number of white blood cells (which can increase the risk of infection)
- Decreased blood levels of magnesium, potassium Hypothyroidism (decrease function of the thyroid gland)
- Increased blood level of liver enzymes (which may indicate liver or gall bladder injury)
- Increased blood sugar level, including increased urine glucose, that may require treatment with medication
- Hypersensitivity, drug hypersensitivity, and infusion related reaction associated with chills, decreased blood pressure, increased heart rate, fever, flushing, sweating, nausea, vomiting, and shortness of breath occurring on the day of the infusion
- Pain [including muscle pain, and stomach pain (both upper and lower)]
- Inflammation of the mucous membranes (including in the mouth)
- Weakness, including muscle weakness
- Muscle spasms
- Tremor (shaking)
- Headache, including sinus headache
- Stomach pain (both upper and lower)
- Hair Loss
- Nail disorder (soft nails, abnormal toe nails)
- Dizziness
- Dry mouth
- Abnormal taste
- Itching
- Increased blood pressure
- Shortness of breath
- Dehydration
- Hot flush
- Nosebleed

Rare
- Reaction or pain at the infusion site
- Swollen stomach
- Gastroesophageal reflux (indigestion)
- Hiccups
- Upset stomach
- Inflammation of the nasal passages
- Inflammation of the lip
- Flu-like illness
- Posterior reversible encephalopathy syndrome (high blood pressure associated with loss of balance, convulsions and temporary blindness)
- Increased blood level of urea, thyroid stimulating hormone, lipase and cholesterol
- Decreased blood level of chloride, sodium, albumin and phosphates
- Canker sores in the mouth or mouth ulcer
- Candidiasis (thrush or yeast infection in the mouth or vaginal area)
- Dry eye, eye irritation, redness of the eye, or changes in the surface of the eye
- Blurred vision
- Difficulty in swallowing, painful swallowing
- Difficulty in speaking
- Joint stiffness
- Erectile dysfunction, decreased sex-drive
- Bleeding gums, swollen gums
- Coughing up blood
- Hemorrhage (bleeding)
- Bruising
- Ringing in ears
- Hearing loss
- Chest pain
- Decreased blood pressure
- Abnormal electrocardiogram (fast or irregular heart beat)
- Hypoxia (decreased oxygen to the brain)
- Intestinal ischemia (lack of blood supply to the colon)
- Difficulty in getting to sleep
- Depression
- Numbness and tingling (in the arms and legs or mouth)
- Edema or swelling (including arms and legs)
- Pulmonary embolism (blood clots in lungs)
- Deep vein thrombosis (blood clot in the veins of the arms or legs)
- Kidney failure
- Metabolic acidosis (increased level of acid in the body)
- Increased serum creatinine (which could mean kidney damage)
- Decreased blood sugar level
- Transient Ischemic attack (the result of decreased blood to the brain)
- Feeling sleepy
- Night sweats, sweating
- Infection (including pneumonia)
- Wheezing (difficulty breathing), cough
- Acute pancreatitis (inflammation of the pancreas)
- Septic Shock (resulting in very low blood pressure due to severe infection)
- Rectal abscess
- Inflammation of the intestine
- Hand-foot syndrome (redness, tenderness and peeling of the hands and feet)

Events of clots in blood vessels [or blood clots] have been reported following administration of ganitumab alone and in combination with other anti-cancer therapies. As blood clots are known to be potentially life-threatening, blood clots associated with ganitumab may also be fatal.
Hearing loss has been reported in patients who received as little as one dose of a drug similar to ganitumab. It is believed that this may happen with all antibodies of this type. Mild to moderate hearing loss (or partial loss) has been uncommonly reported after receiving ganitumab. It is not possible to determine whether these reported events are related directly to the administration of ganitumab.

Allergic reactions to ganitumab have been reported, including chills, decreased blood pressure, increased heart rate, fever, flushing, sweating, nausea, vomiting and shortness of breath during or following the administration of ganitumab. If you have symptoms of an allergic reaction, you should contact the study doctor or his/her study staff immediately.

Infusion reactions (side effects that occur during or after the drug is given through the vein) to ganitumab have been reported, including dizziness, difficulty breathing or swallowing, or a decrease in blood pressure. If you have any of these symptoms, you should contact the study doctor or his/her study staff immediately.

After you start taking ganitumab, it is possible that your body may make antibodies (proteins that can cause ganitumab not to work). Subjects have developed a protein against ganitumab (also known as anti-ganitumab antibody). These antibodies may prevent ganitumab from working, although this did not happen in these cases. If you develop antibodies to ganitumab, it is unknown whether these antibodies will harm you in any way. Blood tests will be used to check for antibodies during the study. Reactions at or near the area of the injection have been seen in other people taking ganitumab. Symptoms may include redness, tenderness or pain, bruising, warmth, swelling, itching and/or infection at the injection site. If you have any of these symptoms, you should contact the study doctor or his/her study staff immediately. A skin reaction called erythema multiforme and a skin drug reaction occurred in one subject each after receiving ganitumab in combination with an anti-cancer therapy called everolimus.

Risks and side effects related to gemcitabine include those that are:

**Likely**
- Low blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Nausea
- Diarrhea
- Loss of appetite
- Tiredness
- Fever
- Headache and chills
- Skin rash that may cause itching
- Swelling of the foot, leg, and ankle

**Less Likely**
- Muscle aches
Risks and side effects related to capecitabine include those that are:

**Likely**
- Nausea
- Diarrhea
- Mouth sores
- Loss of appetite and weight loss
- Weakness
- Tiredness
- Redness and/or drying of the skin, especially the hands and feet.
- Skin or nail darkening
- Skin rash or peeling of skin on hands and feet
- Low blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Infection

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

**Rare but serious**
- Chest pain or irregular heartbeat

**Dangerous interaction with warfarin (Coumadin):** If you are taking warfarin (which is also called Coumadin), a medicine used to prevent blood clotting, capecitabine may change the way your blood clots. The interaction between warfarin and capecitabine is very large and could result in severe bleeding. If you need to take warfarin, your study doctor will regularly check for changes in blood clotting time.
Risks and side effects related to the radiation include those that are:

**Likely**
- Stomach pain and intestinal 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
- Permanently dry skin in the radiation treatment area
- Low blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Loss of appetite and weight loss
- Mild muscle aches in the area treated

**Less Likely**
- Vomiting
- Infection

**Rare but serious**
- Change in liver or kidney function, which is unlikely to cause symptoms.
- Bowel obstruction, which could result in abdominal pain, nausea and vomiting and may require surgery.
- Gastric, duodenal or small-bowel ulcer formation that can result in abdominal pain, nausea and vomiting, and bleeding, and may require surgery.

**Reproductive risks:**

It is not known if ganitumab is harmful to an unborn baby. If you have intercourse during this study, you should understand that even with the use of effective birth control there is still a small chance that a pregnancy could occur. Potential risks include loss of the pregnancy (a miscarriage) and birth defects.

You should not become pregnant or father a baby while on this study because the radiation and the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study and for an additional 2 months after the end of the mother’s treatment. It is important you understand that all women on this study need to use birth control during treatment and for an additional 2 months after the end of treatment. Men need to use birth control or abstain during treatment and for an additional 6 months after the end of treatment. If a woman becomes pregnant or suspects she is pregnant during this study or if a man’s partner becomes or suspects she is pregnant during this study, you must tell your study doctor immediately.
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 in the study may make you unable to have children.

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. Although the main goal of the study is to test the safety of ganitumab plus standard treatment, researchers hope this treatment might be better against pancreatic cancer compared to the usual treatment. Even though there is no proof of this yet, we do know that the information from this study will help researchers 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 study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. 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 National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Qualified representatives of Amgen, maker of ganitumab

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At
most, the Web site will include a summary of the results. You can search this Web site at any time.

**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. Amgen, the manufacturer of the study agent, will supply the ganitumab at no charge while you take part in this study. Amgen does not cover the cost of administrating the ganitumab ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won’t happen, it is possible that the manufacturer may not continue to provide the ganitumab for some reason. If no ganitumab is available, no one will be able to get more, and the study would close. If a problem with getting ganitumab occurs, your study doctor will talk to you about it.

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](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 study 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.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

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). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*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 that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.

You can say “yes” or “no” to the following study. Below, please mark your choice.

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

**About Using Tissue and Blood for Research**

You are going to have a biopsy 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.

If you have surgery on your pancreas after you finish treatment, we would also like to keep some of the left over tumor tissue for future research.

Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available at http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm.

In addition, we would like to collect about 2 tablespoons of blood for future research at the following times: before starting treatment, before chemoradiation, and 21-42 days after chemoradiation is completed.

The research that may be done with your tissue and blood 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 and blood will not be given to you or your study 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 and blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue and blood 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 and will be returned to the institution that submitted it and any remaining blood will be destroyed.

In the future, people who do research may need to know more about your health. While the doctor/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 and blood are used for genetic research (about diseases that are passed on in families). Even if your tissue and blood are used for this kind of research, the results will not be put in your health records.

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

**Benefits**
The benefits of research using tissue and blood 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 study doctor or nurse, or call our research review board at __________________________ [IRB's phone number].

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue □Yes □ No
   - Blood □Yes □ No

2. My specimens 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), as follows:
   - Tissue □Yes □ No
   - Blood □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)

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 _____ [insert total of number of pages] 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.
## APPENDIX II STUDY PARAMETER TABLE

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Treatment</th>
<th>During Treatment (see Section 11.2 for further details)</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 days prior to study entry</td>
<td>21 days prior to study entry</td>
<td>14 days prior to study entry</td>
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<tr>
<td>History</td>
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<tr>
<td>Physical with weight and vital signs</td>
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<td>Documentation of history of hearing loss</td>
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<td>Pathologically confirmed disease</td>
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<td>Response Assessment</td>
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<tr>
<td>Performance status</td>
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<td>Within 1 week of enrollment</td>
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<tr>
<td>CT scan with contrast/ MRI of abdomen/pelvis</td>
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<tr>
<td>Pancreatic Protocol CT scan FOR TREATMENT PLANNING</td>
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<tr>
<td>Chest CT or whole-body PET/CT</td>
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<tr>
<td>CBC w/ diff, platelets, ANC</td>
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<td>HgbATC</td>
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<td>CA19-9</td>
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<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
## Appendix II (continued)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Treatment</th>
<th>During Treatment (see Section 11.2 for further details)</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Biliary stent placement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event eval (and as needed based on reporting requirements)</td>
<td></td>
<td>X X X</td>
<td></td>
</tr>
<tr>
<td>Tissue for banking (for consenting patients)</td>
<td></td>
<td>Pretreatment and post-treatment (if post-treatment surgery performed)</td>
<td></td>
</tr>
<tr>
<td>Plasma for banking (for consenting patients)</td>
<td>X</td>
<td>Following induction chemotherapy but prior to chemoRT</td>
<td>21-42 days post chemoRT completion</td>
</tr>
<tr>
<td>Whole blood for banking (for consenting patients)</td>
<td>X (if site misses pretreatment time point, collection may occur at any other time point or follow-up visit)</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX III

**ZUBROD PERFORMANCE SCALE**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
APPENDIX IV

AJCC STAGING SYSTEM

EXOCRINE AND ENDOCRINE PANCREAS

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)
*This also includes the “PanInIII” classification.

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)

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  N1  M0
        T2  N1  M0
        T3  N1  M0
Stage III T4  Any N  M0
Stage IV Any T  Any N  M1
Dual phase pancreas CT protocol using iodinated intravenous contrast will be obtained at 2.5 or 3 mm slice thickness and, if possible, reconstructed to 1.25 or 0.625 mm slice thickness in addition to the 2.5 mm sections or 1.5 and 0.75 mm slice thickness in addition to the 3 mm sections. The two phases are during the phase of peak pancreatic enhancement and during portal venous enhancement and will be obtained of the entire abdomen. If CT cannot be obtained because of allergy to iodinated contrast, gadolinium enhanced MRI will be utilized of the entire abdomen utilizing T1, T2 and dynamically obtained T1 weighted sequences at a slice thickness of maximally 7mm. If patient has history renal insufficiency or renal failure, and calculated GFR within 14 days prior to CT or MRI is < 30, noncontrast MRI will be utilized with T1 and T2 weighted sequences with a slice thickness not to exceed 7mm. If MRI cannot be obtained (i.e. implanted electronic devices), unenhanced 2.5 or 3 mm sections of the abdomen will be obtained by CT without intravenous contrast.

The timing of imaging after contrast administration: Bolus Tracking technique
The timing varies between the 16 and 64 detector scanners. For example, imaging of the entire abdomen during the pancreatic parenchymal phase, in a normal patient with normal cardiac circulation time, on a 16 would be approximately begin at 36 seconds after the start of contrast injection and finish at 46 seconds. On the 64, it would begin at 40 seconds, and end at 45 seconds. (The pancreas is imaged during the same time period for both-- note both terminate at 45-46 seconds). The second phase is at 60 seconds after the start of injection depending on the scanner (60 for 16) in a normal patient.

A standard commercially available intravenous bolus tracking technique is recommended for use to control for variations in cardiac circulation time, to ensure that images are obtained during the correct phases of contrast enhancement. As is standard practice, a cursor is placed in the aorta at the level of the origin of the celiac axis and is used to detect when contrast arrives in the abdominal aorta and raises the density value to 100 Hounsfield Units. The 16 detector row scanner is instructed to begin scanning 16 seconds after that level is reached. Scanning of the abdomen is completed within 10 seconds, and after a subsequent 14 second delay, the abdomen is imaged again during the portal venous phase. In a normal patient, scanning of the abdomen during the first phase would begin 36 seconds after the start of contrast injection, and scanning of the second phase would begin 60 seconds after contrast injection.

In contrast, the 64 detector row scanner is instructed to begin 20 seconds after the 100 HU threshold is reached. Scanning of the abdomen is completed within 5 seconds, and after a subsequent delay of 15 seconds, the abdomen is imaged again during the portal venous phase. In a normal patient, scanning of the abdomen during the first phase would begin 40 seconds after the start of contrast injection, and scanning of the second phase would begin 60 seconds after contrast injection. The differences in timing between the 16 and 64 detector scanner are designed so that imaging of the pancreas during the first phase is finished at approximately 45-46 seconds after the start of contrast injection.
# APPENDIX VI

CAPECITABINE DOSING TABLE BASED UPON BODY SURFACE AREA CALCULATION

## Capecitabine Starting Dose

<table>
<thead>
<tr>
<th>Dose Level 1650 mg/m²/d</th>
<th>AM 150 mg</th>
<th>AM 500 mg</th>
<th>PM 150 mg</th>
<th>PM 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA (m²)</td>
<td>Total Daily Dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.24</td>
<td>2000</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1.25-1.36</td>
<td>2150</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1.37-1.51</td>
<td>2300</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1.52-1.64</td>
<td>2600</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1.65-1.76</td>
<td>2800</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1.77-1.91</td>
<td>3000</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>1.92-2.04</td>
<td>3150</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2.05-2.17</td>
<td>3300</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>&gt;2.18</td>
<td>3600</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose Level 1250 mg/m²/d</th>
<th>AM 150 mg</th>
<th>AM 500 mg</th>
<th>PM 150 mg</th>
<th>PM 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA (m²)</td>
<td>Total Daily Dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.24</td>
<td>1500</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1.25-1.36</td>
<td>1650</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1.37-1.51</td>
<td>1800</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>1.52-1.64</td>
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<td>2</td>
<td>1</td>
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<tr>
<td>1.65-1.76</td>
<td>2150</td>
<td>1</td>
<td>2</td>
<td>0</td>
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<tr>
<td>1.77-1.91</td>
<td>2300</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1.92-2.04</td>
<td>2450</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2.05-2.17</td>
<td>2500</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2.18</td>
<td>2650</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
APPENDIX VII

BIOSPECIMEN COLLECTION INSTRUCTIONS

Shipping Instructions:

US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter St, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter St, Room S341
San Francisco, CA 94115

- Include all RTOG paperwork in pocket of biohazard bag.
- Check that the STF has the consent boxes checked off.
- Check that all samples are labeled with RTOG study and case number, and include date of collection as well as collection time point.

- **FFPE Specimens:**
  - Slides should be shipped in a plastic slide holder/ slide box. Place a small wad of padding in top of container If you can hear the slides shaking they are likely to break during shipping.
  - FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear them shaking they are likely to break during shipping.
  - Slides, Blocks or Plugs can be shipped ambient or with a cold pack either by USPS to the USPS address (94143) or by Courier to the Street Address (94115). Do NOT ship on Dry Ice.

- **Frozen Specimens:**
  - Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80°C until ready to ship.

- For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by email at: RTOG@ucsf.edu or (415)-476-7864 or fax (415)-476-5271
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of plasma, or whole blood:

**Kit contents:**
- One Purple Top EDTA tube for plasma (A)
- One Purple Top EDTA tube for Whole Blood (B)
- Twenty five (25) 1 ml cryovials
- Biohazard bags (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Kit Instructions
- Specimen Transmittal Form
- UN1845 DRY Ice Sticker
- UN3373 Biological Substance Category B Stickers

**Preparation and Processing of Plasma and Whole Blood:**

**A) Plasma (If requested): Purple Top EDTA tube #1**

- Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

**Process:**
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70°C to -90°C.
6. Store frozen plasma -70°C to -90°C until ready to ship on dry ice.
7. See below for storage conditions.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on STF.**

**B) Whole Blood For DNA (If requested): Purple Top EDTA tube #2**

- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “blood”.

**Process:**
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “blood”.
3. Place cryovials into biohazard bag and freeze immediately at -70°C to -80°C Celsius.
4. Store blood samples frozen -70°C to -90°C until ready to ship on dry ice.
5. See below for storage conditions.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on STF.**
Storage and Shipping:

Freezing and Storage:

☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

☐ Store at −80°C (−70°C to −90°C) until ready to ship.
  If a -80°C Freezer is not available, Samples can be stored short term in a -20°C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).
  - OR:
    ▪ Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).
  - OR:
    ▪ Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

☐ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

☐ Ship specimens on Dry Ice overnight **Monday-Wednesday** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.

☐ Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.

☐ Wrap frozen specimens of same type (i.e., all plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice breaking the tubes.

☐ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

☐ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.

☐ For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271

**Shipping Address:** FedEx/UPS/Courier address (For all frozen samples)

RTOG Biospecimen Resource at UCSF
2340 Sutter St, Room S341
San Francisco, CA 94115

Contact Phone 415.476.7864