RADIATION THERAPY ONCOLOGY GROUP

RTOG 0848

A PHASE III TRIAL EVALUATING BOTH ERLOTINIB AND CHEMORADIATION AS ADJUVANT TREATMENT FOR PATIENTS WITH RESECTED HEAD OF PANCREAS ADENOCARCINOMA

NCI-Supplied Agent: Erlotinib (NSC#718781; IND 63383)
NCI will not be supplying erlotinib to EORTC sites (see Appendix XII)

Study Chairs

RTOG

Principal Investigator
Radiation Oncology
Ross A. Abrams, MD
Rush University Medical Center
500 S. Paulina, Atrium Bld, Suite 013
Chicago IL 60612-3833
312-942-5771/FAX312-563-8656
Ross_a_abrams@rush.edu

Radiation Oncology
William Regine, MD
University of Maryland School of Medicine
22 South Greene Street
Baltimore, MD 21201
410-328-2331/FAX:410-328-6911
wregine@umm.edu

Radiation Oncology
Karyn A. Goodman, M.D
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021
212-639-3983/FAX 212-
goodmank@mskcc.org

Medical Oncology
Howard Safran, MD
Brown University Oncology Group
168 Summit Ave
Providence RI, 02906
401-793-7151/ FAX401-793-4049
hsafran@lifespan.org

SWOG

Medical Oncology
Lab Correlatives
Philip A Philip, MD, PhD, FRCP
Karmanos Cancer Inst
Wayne State University
4th FL HWRC, 4100 John R
Detroit MI, 48201
313-576-8728/FAX 313-576-8729
philipp@karmanos.org

Surgical Oncology
Andrew M. Lowy, MD
Univ of CA San Diego
Moore Cancer Ctr
3855 Health Sciences Dr
MC0987
La Jolla, CA 92093-0987
858-822-2124/FAX 858-534-4813
alowy@ucsd.edu

Statistician, Lab Correlatives
Jacqueline Benedetti, Ph.D.
SWOG Statistical Center
Fred Hutchinson Cancer Research Center
PO Box 19024
1100 Fairview Ave N #M3-C102
Seattle Wa 98109
206-667-6443/FAX 206-667-4408
jbenedet@fhcrc.org

Pathology
Jining Feng, MD, PhD
Department of Pathology
Wayne State University
3990 John R Street
Detroit, MI 48201
313-745-8556/FAX313-745-9299
jfeng@dmc.org

EORTC

EORTC Chair,
Lab Research, Pathology
Manfred P. Lutz, MD
Caritasklinik St Theresia
Medizinische Lkinik, Rheinstr 2
Saarbrucken 66113, Germany
(49) 681-4061001/FAX (49) 681-4061003
m.lutz@caritasklinik.de

Radiation Oncology
Karin Haustermans, M.D.
Kliniekhoofd Radiotherapie Oncologie
Leuvens Kankerinstituut
UZ Leuven | campus Gasthuisberg | Herestraat 49 | B - 3000 Leuven
+32 16 34 69 02/Fax +32 16 34 69 05
karin.haustermans@uzleuven.be

Medical Oncology
Jean-Luc Van Laethem, MD
Erasme Univ Hospital
808 Lennik Street
Brussels B-1070
(32)255-53712/FAX (32) 255-54697
JL.Vanlaethem@erasme.ulb.ac.be

Medical Physics
Coen Hurkmans, PhD
Department of Radiotherapy
Catharina Hospital
P.O. Box 1350
5602 ZA Eindhoven
The Netherlands
(0031) 40 2396493 / 6400
Coen.Hurkmans@cze.nl

RTOG Study Chairs
(Continued)

Medical Oncology
Malcolm Moore, MD
Princess Margaret Hospital
610 University Avenue 5-708
Toronto ON M5G 2M9 Canada
416-946-2263/FAX 416- 946-2082
malcolm.moore@uhn.on.ca

Surgical Oncology
Adam Berger, MD
Thomas Jefferson University
1100 Walnut St, Medical Ofc Bldg Fl 5
Philadelphia PA, 19107
215-503-6302/FAX 215-922-8222
adam.berger@jefferson.edu

Translational Research
Chandan Guha, MD, PhD
Albert Einstein College of Medicine
350 Sprain Rd, Scarsdale NY 10583
941-479-5610/FAX 781-231-5064
cguhamd@pol.net

Quality of Life
Lisa Kachnic, MD
Boston Medical Center
830 Harrison Avenue, LL
Boston, MA 02118
617-638-7057/FAX 617-638-7144
lisa.kachnic@bmc.org

Medical Physics
Michael Gillin, PhD
MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 94
Houston, TX 77030
713-563-2507/FAX713-563-2545
mgillin@mdanderson.org

Statistician
Kathryn Winter, MS
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19103
215-574-3198/FAX 215-928-0153
kwinter@acr.org

Document History

	Version/Update Date	Broadcast Date
Update	April 12, 2012	April 12, 2012
Amendment 3	May 23, 2011	June 14, 2011
Update	June 17, 2010	June 17, 2010
Amendment 2	June 8, 2010	June 17, 2010
Amendment 1	March 4, 2010	March 25, 2010
Update	November 17, 2009	November 17, 2009
Activation	October 28, 2009	November 17, 2009

RTOG Headquarters/Department of Statistics
215-574-3189
1-800-227-5463, ext. 4189

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The following Cooperative Groups have endorsed this trial via the CTSU Endorsement Plus Option: SWOG: Co-chair Philip A. Philip, MD. SWOG members will enroll patients to this study via the Cancer Trials Support Unit (CTSU). Institutions holding dual memberships in SWOG and RTOG may credit either Group for enrollments, provided the credited PI is a member of the credited Group.

(4/12/12) The following Cooperative Groups have endorsed this trial:

ECOG: Co-Chair Anuradha Bapsi Chakravarthy, MD. ECOG members will enroll patients to this study via the Cancer Trials Support Unit (CTSU)

CALGB: Co-Chair Eileen O'Reilly, MD. **CALGB members will enroll patients to this study via the Cancer Trials Support Unit (CTSU)**

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with RTOG 0848 will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be submitted to RTOG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the RTOG data center.

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0848
A Phase III Trial Evaluating Both Erlotinib and Chemoradiation as Adjuvant Treatment for Patients with Resected Head of Pancreas Adenocarcinoma

SCHEMA

FIRST RANDOMIZATON

STRATIFY

Nodal Status:
1: involved
2: uninvolved

CA19-9 result:
1: ≤ 90
2: > 90 – 180

Surgical margins:
1: positive (R1)
2: negative (R0)

RANDOMIZE

Arm 1:
Gemcitabine x 5 cycles

Arm 2:
Gemcitabine + Erlotinib x 5 cycles

Evaluate to Confirm No Progression

If no progression, then:

STRATIFY

First Randomization Treatment Arm:
1. Arm 1gemcitabine vs.
2. Arm 2gemcitabine + erlotinib

SECOND RANDOMIZATON
For Non-Progressing Patients

RANDOMIZE

Arm 3:
1cycle of chemotherapy

Arm 4:
1 cycle of chemotherapy followed by XRT with either capecitabine or 5-FU

NOTE: It is mandatory that the treating physician determine radiation therapy technique (3D-CRT or IMRT) that will be used prior to re-registering the patient.
XRT treatment plan to be submitted for review no sooner than 7 days and no later than 14 to 21 days after second randomization AND completion of first chemotherapy cycle of ARM 4
RT treatment plan must be APPROVED prior to XRT start.

Patient Population: (See Section 3.0 for Eligibility)
Resected head of pancreas adenocarcinoma. This includes the pancreatic head, uncinate process, and neck of the pancreas, status post a curative-intent pancreaticoduodenectomy

Required Sample Size: 950

RTOG Institution # _____

RTOG 0848 **ELIGIBILITY CHECKLIST—STEP 1 (5/23/11)**

Case # _____ (page 1 of 3)

_____ (Y) 1. Histologic proof of primary head of pancreas invasive adenocarcinoma managed with a potentially curative resection (i.e., removal of all gross tumor) involving a classic pancreaticoduodenectomy (Whipple) or a pylorus preserving pancreaticoduodenectomy.

_____(Y) 2. Does the operative report contain a statement from the surgeon documenting that a total gross excision of the primary tumor was achieved?

_____ (Y) 3. AJCC 6th edition pathologic stage T1-T3, N0-1, M0?

_____ (Y) 4. Does the pathology report document all margins including the status of the three major surgical margins (bile duct, pancreatic parenchyma, and retroperitoneal [uncinate]) and document the size of the primary tumor?

_____ (Y) 5. Abdominal/pelvic CT scan with contrast (or MRI if allergic to contrast) and either chest CT or chest x-ray within 31 days of study entry?

_____(Y) 6. Is the patient's Zubrod performance status 0 or 1?

_____(Y) 7. Do the patient's laboratory values meet the criteria in Section 3.0?

_____(Y) 8. Is the patient's total oral caloric intake ≥ 1500 calories/day?

_____(Y) 9. Is the patient willing to practice adequate contraception while on study (women of childbearing potential and men)?

_____(Y) 10. Post resection serum CA19-9 ≤ 180 IU/L within 21 days of registration on study?

_____(N) 11. Has the patient had prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

_____(N) 12. Has the patient had prior systemic chemotherapy for the study cancer?

_____(N) 13. Has the patient undergone total pancreatectomy, distal pancreatectomy or central pancreatectomy?

_____(N) 14. Does the patient have coexistent medical condition that would preclude protocol therapy (as outlined in Section 3.2)?

_____(N) 15 Is the patient pregnant or lactating?

(Continued on next page)

ELIGIBILITY CHECKLIST—STEP 1 (6/8/10)
(page 2 of 3)

_____(N/Y) 17. Has the patient had prior invasive malignancies, except for non-melanomatous skin cancers? (Patients with a history of carcinoma in situ are eligible.

_____(Y) If yes, has the patient been disease free for ≥ 2 years?

_____(Y) 18. Has a radiation oncologist evaluated this patient and agreed and documented that patient is suitable to receive radiotherapy as administered in this protocol?

_____(N,Y) 19. Does the patient have active HIV infection?

_____(Y) If yes, is the CD4 count ≥ 499/cu mm and a viral load ≤ 50 copies/ml?

_____(Y) 20. Age ≥ 18?

_____(Y) 21. Interval between definitive tumor-related surgery and 1st step registration between 21-56 days?

The following questions will be asked at Step 1 Study Registration:

3D-CRT and IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____ 1. Institutional person registering case

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible for this study?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Patient's ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

(Continued on next page)

ELIGIBILITY CHECKLIST—STEP 1 (6/8/10)

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of payment

_____ 15. Any care at VA or military hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization date: This date will be populated automatically.

_____ 18. Medical oncologist's name

_____(Y/N) 19. Patient has given permission to keep sample(s) for use in future research to learn about, prevent, or treat cancer

_____(Y/N) 20. Patient's Initial Consent given for specimen use for research unrelated to the patient's cancer?

_____(Y/N) 21. Did patient consent to future contact about more research?

_____(Y/N) 22. If randomized to radiation, is there a possibility that this patient will be treated with IMRT?

_____ 23. Nodal status: involved vs uninvolved?

_____ 24. CA 19-9: ≤ 90 vs > 90-180

_____ 25. Surgical margins: positive (R1) vs negative (R0)?

_____(N/Y) 26. Patient has consented to take part in the quality of life study?

_____ If no, provide reason:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

_____(Y/N) 27. Tissue/Blood obtained at progression (if occurs) kept for cancer research?

_____(Y/N) 28. Tissue/Blood obtained at progression (if occurs) kept for medical 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 _____

RTOG Institution #
RTOG 0848
Case #

ELIGIBILITY CHECKLIST STEP 2 REGISTRATION (A2) (6/8/10)

_____ 1. Institutional person registering

_____(Y/N) 2. Patient able to continue protocol treatment

_____(1,2,3,4) 3. If no, provide reason
   1. Progression of disease
   2. Patient refusal
   3. Did not start 5th cycle (Gem ± erlotinib)
   4. Other,Specify_____

_____ 4. Patients initials (Last, First)

_____ 5. Verifying physician

_____ 6. Patient ID#

_____ 7. Calendar Base Date

_____ 8. Randomization Date

_____(1, 2) 9. First Randomization treatment
   1. Gemcitabine
   2. Gemcitabine + Erlotinib

1.0 INTRODUCTION

1.1 Adjuvant Treatment of Pancreatic Cancer

Despite potentially curative resection for pancreatic adenocarcinoma, the 5-year survival rate in these patients is <20%. [Nitecki, 1995; Piorkowski, 1982; Gudjonsson, 1987] The pattern of failure demonstrates both a significant component of local-regional relapse (50%-85%) and distant liver / intraabdominal failure.[Gudjonsson, 1987; Tepper, 1976] Adjuvant treatment is used to attempt to prevent recurrence and improve survival.

1.2 Does Adjuvant Chemoradiation Improve Survival?

1.2.1 The GITSG Experience

The Gastrointestinal Tumor Study Group (GITSG) performed a small, randomized trial that demonstrated an improvement in survival for patients receiving adjuvant 5-FU chemoradiation followed by maintenance bolus 5-FU compared to surgery alone.[Kalser, 1985] Twenty-one patients receiving adjuvant 5-FU chemoradiation followed by additional 5-FU had a median survival of 21 months and 5-year survival of 19% compared with 11 months and 5%, respectively, for patients undergoing surgery alone (p = 0.03).

1.2.2 EORTC Trial

In an effort to reproduce the findings reported by the GITSG, a study sponsored by the European Organization for Research and Treatment of Cancer (EORTC) randomly assigned 114 patients with resected pancreatic cancer to receive either postoperative concurrent 5-FU (25 mg/kg per day by continuous infusion) and radiotherapy (40 Gy, split course) or observation. Postoperative chemoradiotherapy was associated with a trend toward improvement in median survival and 2-year survival that did not reach statistical significance (26% versus 34% for control and treated patients, respectively, p = 0.099). [Klinkenbijl, 1999]

1.2.3 ESPAC-1

Worldwide, the administration of adjuvant radiation remains controversial. The European Study Group for Pancreatic Cancer –1 (ESPAC-1) trial was a phase III, postoperative adjuvant trial that sought to determine the role of adjuvant chemotherapy and chemoradiation. This trial demonstrated a favorable impact of chemotherapy but a detrimental effect of chemoradiation.[Neoptolemos, 2001; Neoptolemos, 2004] However, the conclusions of ESPAC-1 are controversial because of trial design and execution concerns.[Abrams, 2001] A 62% local recurrence rate was reported in the ESPAC trial. Similar high local recurrence rates have been reported in multiple other adjuvant trials.[Griffin, 1990]

1.2.4 RTOG 9704

RTOG 9704 was the first United States cooperative group adjuvant pancreatic trial in three decades. It was designed to evaluate whether the addition of gemcitabine to 5-FU−based chemoradiation improved survival for patients with resected pancreatic adenocarcinoma when compared to only a 5-FU systemic therapy regimen. Patients with resected pancreatic adenocarcinoma were randomized to receive either 5-FU (continuous infusion at 250 mg/m^2/day) or gemcitabine (1000 mg/m^2 IV weekly) pre- and post-chemoradiation. [Regine, 2008] Both groups of patients were given chemotherapy over 3 weeks of pre- and 12 weeks post-chemoradiation. Chemoradiation was the same for all patients (daily fractions of 1.8 Gy, 5 days/week for 5.5 weeks, for a total of 50.4 Gy, with continuous infusion 5-FU). Grade 4 hematologic toxicity was 2% in the 5-FU arm and 14% in the gemcitabine arm (p<0.0001), without difference in the rates of febrile neutropenia/infection. There were no differences in the ability to complete chemotherapy (86%, 5-FU vs. 90%, gemcitabine) or radiation (85%, 5-FU vs. 88%, gemcitabine).

Overall survival and survival among patients with lesions of the pancreatic head (descriptor used for periampullary pancreatic lesions) were the primary endpoints of the study. A total of 451 patients were randomized, eligible, and analyzable. Patients with pancreatic head tumors (n = 381) experienced improved survival, with median and 3-year survival of 20.5 months and 31% for the gemcitabine arm vs. 16.9 months and 22% for the 5-FU arm (p=0.09; HR=0.82, CI=0.65 -1.03). Pretreatment CA19-9 level > 90 IU/l strongly predicted survival. The median and 3-year overall survival for patients with CA 19-9 ≤ 90 were 22.8 months and 33% versus 9.6 months and 2% for patients with CA 19-9>90 (p <0.0001), respectively. The median and 3-year survival in patients in the gemcitabine arm who received radiation according to protocol requirements were 25.2 months and 46%, respectively.

The pattern of tumor relapse was recorded on the site of the first relapse only and categorized as local, regional, or distant. The distribution of relapse was similar among all patients and among patients with pancreatic head tumors. Local relapse occurred in 28% of patients in the 5-FU arm and 23% in the gemcitabine arm. Regional relapse was similar in both arms at 7%-8%. Distant relapse was > 70% in both arms.

This trial compared favorably with the outcome in similar phase III trials in patients with pancreatic adenocarcinoma. This was despite the greater proportion of patients with T3 disease, lymph node positive disease, and microscopically positive margins when compared to GITSG and EORTC trials. In RTOG 9704, 75% of patients had T3 disease, 66% had lymph node positive disease, and 60% had microscopically positive or unknown margins. In the GITSG study only patients with negative surgical margins were included and 28% had lymph node positive disease. In the EORTC study, only patients with T1/T2 disease were included, 50% had lymph node positive disease, and only 23% had microscopically positive or unknown margins. In the CONKO trial, patients were required to have a preoperative CA 19-9 level <2.5 times the upper limit of normal.

1.2.5 Hopkins and Mayo Clinic Analysis

At the 2008 GI Cancer symposium, a collaborative study was reported evaluating the effect of adjuvant chemoradiation from the Johns Hopkins Hospital and the Mayo Clinic and later published as full manuscripts.[Hsu, 2008] The study consisted of 1,045 patients with resected pancreas cancer; 530 (50.7%) received 5-fluorouracil/XRT. Cox proportional hazards models were used with covariates age, sex, institution, margin status, node status, differentiation, surgery type, and T-stage. Overall survival was longer with adjuvant chemoradiation; median overall survival was 22.5 versus 16.3 months, respectively (P<0.001). After adjustment for covariates, adjuvant chemoradiation was associated with improved survival among all patients (univariate RR=0.71, multivariate RR=0.62, p<0.001) and in all sub-groups (multivariate RR=0.54 to 0.74, P<0.05). Therefore, adjuvant chemoradiation was significantly associated with improved survival after resection, regardless of age, tumor size, margin status, node status, and tumor differentiation.

Currently, the use of adjuvant radiation for patients with resected pancreatic cancer represents one of the most contentious and passionate debates in gastrointestinal oncology. ***We hypothesize that this North American/European trial will definitively demonstrate that adjuvant radiation with concurrent fluoropyrimidine will increase survival for patients with resected head of pancreas adenocarcinoma who remain disease free after adjuvant chemotherapy with gemcitabine (or gemcitabine and erlotinib).***

1.2.6 Radiation Issues and Quality Control

The RTOG performed a secondary analysis of RTOG 9704 based on radiation therapy quality assurance (RTQA). Of 416 patients analyzed for RTQA, 216 (52%) had radiation per protocol and 200 (48%) were less than per protocol.[Abrams, 2008] The frequency of per protocol and not per protocol did not differ by treatment arm (per protocol = 55% on 5-FU arm and 48% on gemcitabine arm). Based on the per protocol versus not per protocol radiation delivery, the frequency of grade 3/4 toxicity did not vary significantly on the 5-FU arm but did show a trend of less toxicity for patients on the gemcitabine arm. Survival was significantly increased for patients treated per protocol (p=0.019).

Based on the above analysis, this study will have prospective radiation quality control built into the trial. **The second randomization (-/+ fluoropyrimidine sensitized radiotherapy) will occur after the first 5 cycles of adjuvant systemic therapy.** Patients will be randomized to receive either one additional cycle of systemic therapy *or* one additional cycle of systemic therapy followed by chemoradiation. Radiation will be initiated within 21 days of the last treatment of gemcitabine ± erlotinib. This design will give sufficient time for prospective radiation quality control to prevent a large gap between completion of chemotherapy and initiation of chemoradiation. During this period, radiation treatment plan will be required to be prospectively reviewed by senior RTOG and EORTC radiation oncologists (RTOG: Drs. Ross Abrams and William Regine; EORTC: Drs. Karin Haustermans, and Oscar Matzinger).

1.3 Can the Addition of Adjuvant Erlotinib to Gemcitabine Improve Survival?

1.3.1 Gemcitabine in Pancreatic Cancer

Gemcitabine is considered the most active cytotoxic drug for pancreatic cancer. In a randomized trial of 126 patients with advanced pancreatic cancer, the median and 1-year survival for patients treated with gemcitabine was 5.7 months and 18%, compared with 4.4 months and 2% for patients treated with 5-FU ($p = 0.0025$), respectively.[Burris, 1997]

1.3.2 CONKO-1 – Adjuvant Gemcitabine Improves Survival

A multinational German trial (the CONKO-1 trial) randomly assigned 368 patients with a preoperative CA 19-9 level <2.5 times the upper limit of normal to gemcitabine (1000 mg/m^2 days 1, 8, and 15 every 4 weeks for 6 months) or no treatment after surgery. [Oettle, 2007] Patients were stratified by resection margins (which were positive in 19% of those assigned to gemcitabine and 16% of the control group), tumor size, and nodal status. The primary endpoint was disease-free survival. Median disease-free survival was 13.4 months in the gemcitabine group (95% confidence interval, 11.4-15.3) and 6.9 months in the control group (95% confidence interval, 6.1-7.8; $p < 0.001$, log-rank). Estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group and 7.5% and 5.5% in the control group, respectively. Subgroup analyses showed that the effect of gemcitabine on disease-free survival was significant in patients with either R0 or R1 resection. There was no difference in overall survival between the gemcitabine group (median, 22.1 months; 95% confidence interval, 18.4-25.8; estimated survival, 34% at 3 years and 22.5% at 5 years) and the control group (median, 20.2 months; 95% confidence interval, 17-23.4; estimated survival, 20.5% at 3 years and 11.5% at 5 years; $p = 0.06$, log-rank). An update of study outcome presented in ASCO 2008 demonstrated a significant median and 3-year survival advantage in the gemcitabine group (median 22.8 versus 20.2 months, $p = 0.005$, five-year survival 21 versus 9 percent). [Neuhaus, 2008]

1.3.3 Erlotinib in Pancreatic Cancer

Erlotinib is an orally administered quinazoline, tyrosine kinase inhibitor with potent, reversible inhibitory effects on the EGFR receptor related tyrosine kinases. The National Cancer Institute of Canada trial PA.3 evaluated the combination of erlotinib and gemcitabine versus gemcitabine alone.[Moore, 2007a] In this phase III trial of 569 patients, 25% had locally advanced disease and 75% had distant metastases. Patients were randomized to receive standard-dose gemcitabine, 1000 mg/m^2/week for 7 of 8 weeks followed by 3 out of every 4 weeks plus either erlotinib or placebo. The erlotinib dose in this trial was started at 100 mg daily and the plan was to escalate the dose to 150 mg daily on the first prescheduled interim toxicity analysis. Secondary to the high accrual rate only 23 patients were entered at the higher dose.

The addition of erlotinib to gemcitabine was associated with a significant increase in the 1-year (24% versus 17%) and median survival (6.4 vs. 5.9 months) when compared with single-agent gemcitabine.[Moore, 2007a] A significant improvement in performance status was also observed. The incidence of adverse events were comparable in both arms with the exception of rash (72% vs. 29%), diarrhea (56% vs. 41%), and stomatitis (23% vs. 14%), which were more commonly observed in the erlotinib/gemcitabine arm. The development of a rash from erlotinib predicted significantly improved survival. Patients developing a grade 2 rash had a 10.5 month median survival and a 1-year overall survival of 43%.

Agents that have proven benefit in the metastatic setting should be evaluated in earlier-stage disease where the magnitude of observed benefit may be increased. For example, in the metastatic/locally advanced context gemcitabine achieved only a 4-week improvement in median survival compared to fluorouracil. However, in the adjuvant context gemcitabine increased median survival by 2.6 months (10 – 11 weeks) in the CONKO-001 trial. The earlier-stage disease, with its lower tumor burden and greater sensitivity to therapy, may demonstrate a better proportional benefit. Furthermore, a confirmatory phase III trial of erlotinib in pancreatic cancer would give us confidence investigating the addition of other agents to EGFR tyrosine kinase inhibitors in pancreatic cancer as part of multitargeted therapies. The inclusion of correlative science to study the mechanisms of resistance to erlotinib provides a unique opportunity to understand mechanisms of resistance to anti-EGFR agents.

As reviewed above, for patients with metastatic disease, while erlotinib increased median survival by only 2 weeks, the 1-year survival with erlotinib increased by a relative increase of

40% (from 17%-24%) for patients with metastatic pancreatic cancer. ***We hypothesize that the addition of erlotinib to adjuvant gemcitabine will increase survival for patients with resected head of pancreas adenocarcinoma and that the magnitude of the benefit of erlotinib will increase over time of follow-up by at least the same relative increase as previously demonstrated for patients with metastatic disease.***

1.4 EGFR as Treatment Target: Molecular Determinants of Drug Sensitivity

Erlotinib is the only targeted therapy that has been shown to exert a significant, but minor, effect on survival in metastatic pancreatic cancer by blocking EGFR signaling. There is therefore a rationale to understand the biology of EGFR activation and its association with anti-EGFR treatment outcome.

Recent data indicate a role for Ras mutations in response to anti-EGFR therapies in other tumor types, such as lung and colorectal cancers.[Eberhard, 2005] However, the contribution of such mutations in the outcome of treatment in pancreas cancer remains unknown despite the high frequency of K-Ras mutations in this disease. In pancreatic cancer, K-Ras mutations have been demonstrated in approximately 70%-80% of patients.[Baselga, 2008;Moore, 2007b] The effect of K-Ras mutations on response to erlotinib is uncertain in pancreatic cancer. Investigators from Johns Hopkins tested the hypothesis that global activation of the EGFR pathway is predictive of EGFR inhibitor efficacy. Pancreatic cancer tumors directly xenografted at surgery were treated with the EGFR inhibitors erlotinib and cetuximab and analyzed for biological features.[Jimeno, 2008] Two of 10 tumors were sensitive, and by global gene expression profiling with gene set enrichment analysis, the EGFR pathway was highly expressed in sensitive compared with resistant tumors. EGFR and K-Ras mutations were neither predictive nor responsible for the EGFR pathway activation. Therefore, coordinated overexpression of the EGFR pathway, and not K-Ras mutations, may predict susceptibility to EGFR inhibitors in pancreatic cancer.

Pancreas cancer cells are characterized by multiple genetic mutations that challenge the success of targeting a single pathway, such EGFR, in successful anti-cancer therapy for this disease. Clinical studies have concluded that the expression of EGFR protein that is measured by immunohistochemistry is insufficient and unable to predict response to anti-EGFR therapy. Our proposal therefore includes the study of molecular changes that may closely mimic the activated pathway based on downstream effector molecules such as MAPK, Akt, NFkB, and EGFR ligands. EGFR mutations similar to those found in lung cancer that may predict sensitivity to erlotinib have not been demonstrated in this disease.

There is evidence that epithelial to mesenchymal transition (EMT) limits sensitivity to anti-EGFR therapies.[Jimeno, 2008] Biomarkers associated with EMT status (e.g., E-Cadherin, vimentin) have been reported to be predictors of EGFR inhibitor sensitivity in several human cancer cells including non-small cell lung cancer, in xenografts, and patients samples.[Buck, 2007;Thomson, 2005] EMT may also be a factor in resistance to gemcitabine therapy based on some early preclinical work.[Shah, 2007] Multiple genetic mutations can be responsible and/or associated with EMT including K-Ras and C-Met.

Identification of biomarkers that predict anti-EGFR therapy outcome will influence new drug development in pancreas cancer. The data obtained in the adjuvant setting from this study will help develop biomarkers that will be used in the selection of patients undergoing anti-EGFR therapy for early and advanced stages of pancreas cancer. Moreover, such data may be applicable to other cancers. Identification of a biological role of such biomarkers (e.g., EMT and K-Ras) will lead to the development of targeted therapies against these molecules that can also be applied in therapies for advanced disease.

There is also a need to define mechanisms of resistance to erlotinib and gemcitabine and identify molecules that may be targeted to modulate resistance to therapy. For example, evidence from in vitro assays suggests that drug-resistant pancreatic tumor cells are associated with EMT, a more-aggressive and invasive phenotype in several solid tumors.[Thiery, 2003] Other changes, such as the increased phosphorylation of c-Met, may also be related to chemoresistance through its effect on EMT.

1.5 MicroRNA (5/23/11)

miRNAs play important roles in many normal biological processes; however, the aberrant miRNA expression and its correlation with the development and progression of cancers is an emerging field. Therefore, miRNAs could be used as biomarkers not only for diagnosis of pancreas cancer but also in prediction of prognosis. Importantly, some miRNAs could regulate the formation of cancer stem cells and the acquisition of epithelial-mesenchymal transition, which are critically associated with drug resistance as has been discussed above. Moreover, some miRNAs could target genes related to drug sensitivity, resulting in the altered sensitivity of cancer cells to anti-cancer drugs. We compared the expression profile of microRNAs in the plasma of patients diagnosed with pancreas cancer (n=50) and compared with healthy volunteers (n=10). Data was further validated by quantitative real-time PCR and cell-based assays. Thirty-seven miRNAs were down-regulated and 54 were up-regulated in plasma from patients with PC. The expression of miR-21 was significantly higher, and the expression of let-7 family (especially let- 7d) and miR-146a was significantly lower. Most interestingly, the expression of miR-21 was correlated with worse survival, and the expression of let-7 was inversely correlated with survival in this pilot study with mixed patient population. Moreover, we found that miR-21 family was markedly over-expressed in chemo-resistant pancreas cancer cell lines, which was consistent with the plasma data from patients. Our previous studies have shown increased expression of miR-21 with concomitant loss of PTEN expression in PC cells, which is consistent with our current findings showing the loss of three additional targets of miR-21 (PDCD4, Maspin and TPM1). These results suggest that identifying and validating the expression of miRNAs could serve as potential biomarker for tumor aggressiveness, and such miRNAs could be useful for the future of drug development (Ali 2011).

1.6 Rationale to Limit Patient Enrollment to Patients with Head of Pancreas Adenocarcinoma

Eighty to eighty-five percent of all pancreatic adenocarcinomas arise to the right of the superior mesenteric vein and artery and are resected by a pancreaticoduodenectomy. This anatomic part of the pancreas is the head of the pancreas. It is also often referred to as the periampullary part of the pancreas. The pancreatic neck and uncinate process are also part of the pancreatic head. This is in contradistinction to the parts of the pancreas arising to the left of the superior mesenteric artery, generally known as the body and tail of the pancreas (see figure).

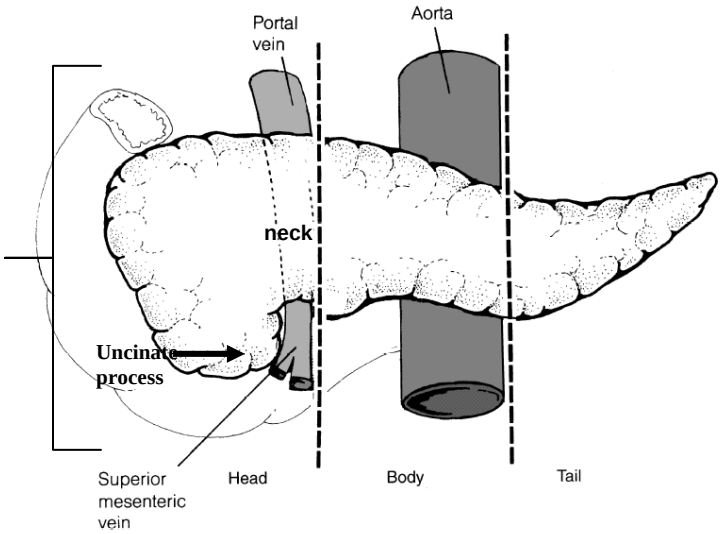

Fig. 18.1. Tumors of the head of the pancreas are those arising to the right of the superior mesenteric–portal vein confluence.

(Figure from AJCC web page accessed at www.cancerstaging.org/education/tnmschema on January 8th, 2009)

The decision to limit enrollment to head of pancreas lesions was made based on the following considerations:

a. This is the group of patients for whom most data and past experience in adjuvant therapy are available.
b. The role of chemoradiotherapy in the adjuvant management of patients with body and tail lesions is even more uncertain than for patients with head of pancreas adenocarcinoma; in RTOG 9704 it appeared that only patients with pancreatic head lesions benefited from gemcitabine.
c. Both the operation required and the regions treated with radiation are substantially different for body and tail lesions as opposed to pancreatic head lesions. Therefore, exclusion of patients with body and tail lesions removes potentially important sources of patient heterogeneity that may be relevant to the chemotherapy and chemoradiation questions being asked.
d. Body and tail pancreas cancers may be biologically different than those arising in the head of the pancreas with earlier micrometastases, thereby limiting the benefit of locoregional therapy.

1.6.1 Implication and Importance of Limiting Patient Enrollment to Patients With Head of Pancreas Adenocarcinoma

There are four adenocarcinomas for which a pancreaticoduodenectomy can be an appropriate operation done with curative intent. These are adenocarcinoma of pancreas, distal common bile duct, proximal duodenum, and the true ampulla However, the non-pancreatic adenocarcinomas are less common than the pancreatic adenocarcinomas and the prognoses associated with pancreaticoduodenectomy for these other three, non-pancreatic sites, especially the duodenum and ampulla, are significantly different (better) than those seen with pancreaticoduodenectomy for head of pancreas adenocarcinoma [Yeo, 1997]. Therefore, this protocol is specifically limited to head of pancreas adenocarcinoma.

1.7 Requirement for clear designation of tumor margin status

RTOG 9704 had a 23% and 26% unknown margin rate in the 5-FU and gemcitabine arms, respectively. The major cause of this designation was the absence of a clear statement within the operative report as to the status of the visible margins, especially the SMA or uncinate margin. The definition of margin status is of crucial importance prognostically. This has been widely recognized and described [AJCC, 2006; Staley, 2006; Raut, 2007; CAP, 2009].The distinction among R0, R1, and R2 resections helps to capture this information nicely. However, since the SMA margin (also known as the uncinate margin), is typically down to the adventitia of the superior mesenteric artery (SMA) which cannot be resected, the only way for the status of this margin to be documented is for the surgeon to document whether there was or was not visible tumor left behind on the surface of the SMA at the conclusion of the operation. This distinguishes between R0 and R1 resections on the one hand (no **visible** tumor left behind, without or with microscopically positive margin) and R2 resections (visible tumor remaining within patient) on the other hand. Pathology reports will be reviewed by the surgical oncology protocol chairs and the EORTC pathology chair (Dr. Andrew Lowy, Dr. Adam Berger and Dr. Manfred Lutz) for interpretation of margin status. If margin status is uncertain from the pathology report, the surgical chairs will speak directly with the submitting surgeon and pathologist to clarify margin status prior to study enrollment. Standardized reporting of the pathology information is encouraged. An example of a standardized reporting form from the College of American Pathologists webpage (www.cap.org/apps on January 8, 2009) in Appendix V.

1.8 Quality of Life/Patient-Reported Outcomes

1.8.1 Importance of Patient-reported Outcomes in Pancreas Cancer

Patient-reported outcomes, in addition to overall survival, are now accepted by oncologists as an important clinical endpoint in phase III trial design for patients with advanced pancreatic cancer. This is largely based on the landmark randomized trial of Burris et.al.[Burris, 1997], which reported, for patients with advanced pancreatic cancer, a significant increase using gemcitabine (rather than fluorouracil) in the “clinical benefit response” that included non-traditional measures related to symptoms, including pain, performance status and weight [Burris, 1997]. To date, there has been limited available literature using formal patient reported measures for patients with pancreatic cancer [Rocha Lima, 2004]. This is unfortunate, because the majority of patients with this cancer have incurable disease and palliation and quality of their remaining life become the major goals.

1.8.2 Patient-Reported Fatigue Using FACIT-Fatigue May Predict for Overall Survival in Patients With Pancreatic Cancer

Fatigue has been described as the most frequent and distressing symptom related to cancer and its treatment [Bower, 2005]. The etiology of fatigue, its correlates, and prevalence in the context of pancreas cancer and its treatment are poorly understood. Moreover, patient-reported fatigue may provide important prognostic information for patients with pancreatic cancer. Tracking of this symptom may be useful for management decisions (local and systemic vs. systemic only) and medical monitoring. To this end, recent data from a clinical study of 86 patients with stage II-IV pancreatic cancer and involuntary weight loss explored patient-reported cancer fatigue and overall survival[Robinson, 2008]. In this study population, 28 patients were given gemcitabine plus 3 mg/kg of infliximab (Remicade), 28 received gemcitabine plus 5 mg/kg of infliximab, and 30 were administered gemcitabine plus placebo in a double-blinded, randomized phase II, multicenter setting. Patient-reported outcome (PRO) endpoints included scores from the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue).

The FACIT-Fatigue, version 4, is a 13-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue [Yellen, 1997]. A 5-point intensity type of rating scale (from “not at all” to “very much”) is used. The FACIT-Fatigue is a psychometrically sound instrument and has been widely used to measure fatigue for patients with various chronic illnesses including cancer [Yellen, 1997], as well as for the U.S. general population [Cella, 2002]. Interestingly in this study of advanced pancreatic cancer [Robinson, 2008], a high baseline FACIT–Fatigue score (> 30), indicating low fatigue, was the best predictor of longer overall survival in a stepwise, Cox proportional hazards multiple-regression analysis (HR, 0.47; CI: 0.30–0.74). Fatigue scores predicted survival when a baseline FACIT–F score of 30 was used as the cut-point for defining high and low fatigue. The median overall survival was 9.1 months (CI: 7.2–11.4) for patients having low fatigue (indicated by higher scores [> 30] and 5.2 months (CI: 4.0–7.2) for those with high fatigue (indicated by low score [< 30]), log rank P = 0.002. In fact, patient perception of fatigue was the best predictor of overall survival, in comparison to baseline Karnofsky Performance Status, lean body mass and hemoglobin level. These findings support several features of an a priori clinical-benefit model and as such, warrant confirmation by large prospective trials.

Based in part on Robinson and colleagues’ intriguing data described above [Robinson, 2008], we hypothesize that patients reporting low baseline fatigue, as measured by the FACIT-Fatigue 13 item questionnaire, will experience longer overall survival.

1.8.3 PROMIS-Fatigue : A Novel Short Form Fatigue Scale

Most recently, the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Roadmap initiative (www.nihpromis.org) was initiated. PROMIS is a 5-year cooperative group program of research designed to develop, validate, and standardize item banks to measure patient-reported outcomes (PROs) relevant across common medical conditions, including cancer [Cella, 2007; Garcia, 2007]. Integral to the work of this group, includes the creation of a PROMIS-derived fatigue short form (using limited questions to minimize patient burden) that was developed for ease of use in oncology populations. While the psychometric properties of this 7-question short fatigue scale have been validated in the general population [Garcia, 2007; Lai, 2008], validation in patients with cancer is underway. A “cross-walk” has been successfully developed between the PROMIS fatigue item bank and the PROMIS-Cancer fatigue item bank that produced the short form measure. These two item banks, sharing 54 common items, were linked by equating item parameters using items that held stable psychometric properties between the cancer and general population populations in which they were tested. Results showed that cancer patients reported more severe fatigue (1/3 standard deviation more severe, but the same scale characteristic curve slope) than the general population, which matches clinical expectations [Cella, 2008]

Since the PROMIS-derived fatigue short form and the FACIT-Fatigue were successfully co-calibrated onto the same fatigue measurement continuum by using Item Response Theory model, we hypothesize that similar clinical validity will be demonstrated again. Specifically, the PROMIS-derived fatigue short form scale can be used as a surrogate for the FACIT-Fatigue, and will also be able to predict for overall survival.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine whether the addition of erlotinib to gemcitabine adjuvant chemotherapy improves survival as compared to gemcitabine alone following R0 or R1 resection of head of pancreas adenocarcinoma (including adenocarcinoma of the head, neck, and uncinate process).

2.1.2 To determine whether the use of concurrent fluoropyrimidine and radiotherapy following adjuvant gemcitabine based chemotherapy further enhances survival for such patients who are without evidence of progressive disease after 5 cycles of gemcitabine based chemotherapy.

2.2 Secondary Objectives

2.2.1 To evaluate disease-free survival of adjuvant chemotherapy followed by radiotherapy and concurrent fluoropyrimidine for patients with resected head of pancreas adenocarcinoma who are disease free after 5 cycles of adjuvant chemotherapy.

2.2.2 To evaluate disease-free survival of standard adjuvant gemcitabine chemotherapy with and without erlotinib for patients with resected head of pancreas adenocarcinoma.

2.2.3 To evaluate the disease-free and overall survival of standard adjuvant treatment with and without erlotinib for patients with resected head of pancreas adenocarcinoma by wild-type and mutant K-Ras status.

2.2.4 To evaluate adverse events with and without erlotinib for patients with resected head of pancreas adenocarcinoma.

2.2.5 To evaluate adverse events of adjuvant chemotherapy ± radiation therapy and concurrent fluoropyrimidine for patients with resected head of pancreas adenocarcinoma who are disease free after adjuvant chemotherapy.

2.2.6 To evaluate preoperative cross-sectional imaging of the primary head of pancreas adenocarcinoma in order to determine the frequency with which objective criteria of resectability are present.

2.2.7 To determine the predictive roles of K-Ras mutations and epithelial to mesenchymal transition (EMT) phenotype in response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibition in early-stage pancreas cancer.

2.2.8 To determine the frequency of EGFR activated pathway and its influence on outcome in patients treated with gemcitabine and/or erlotinib, the association between developmental molecular markers and outcome of therapy, the phenotype and genotype of tumors in patients with recurrence after resection.

2.2.9 To determine if patients reporting low baseline fatigue, as measured by the FACIT-Fatigue, predicts survival and to explore correlations between baseline fatigue, as measured by PROMIS, and survival.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility

3.1.1 Histologic proof of primary head of pancreas invasive adenocarcinoma managed with a potentially curative resection (i.e., removal of all gross tumor) involving a classic pancreaticoduodenectomy (Whipple) or a pylorus preserving pancreaticoduodenectomy. Patients with invasive adenocarcinoma that also contains a component of intraductal papillary mucinous neoplasm (IPMN) are eligible

The operating surgeon must document in the operative note that a complete gross excision of the primary tumor was achieved. The pathology report must include documentation of the margin status and the size of the tumor. The pathology report must also include the status of the three major margins—bile duct, pancreatic parenchyma, and retroperitoneal (uncinate).

3.1.2 Interval between definitive tumor-related surgery and 1st step registration between 21-56 days.

3.1.3 Patients will be staged according to the 6th edition AJCC staging system with pathologic stage T1-3, N0-1, M-0 being eligible. Pathologic reporting using the CAPS format is strongly encouraged (see Appendix V).

3.1.4 Age ≥ 18.

3.1.5 Zubrod performance status 0 or 1.

3.1.6 Complete history and physical examination including weight and Zubrod status within 31 days of study entry.

3.1. 7 Before starting therapy the patient should be able to maintain adequate oral nutrition of ≥ 1500 calories estimated caloric intake per day and be free of significant nausea and vomiting.

3.1.8 CBC/differential obtained within 21 days of registration on study, with adequate bone marrow function defined as follows:

3.1.8.1 Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3

3.1.8.2 Platelets ≥ 100,000 cells/mm^3

3.1.8.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.9 Post resection serum CA19-9 ≤ 180 units/mL within 21 days of registration on study.

3.1.10 Patients must have:

3.1.10.1 Serum total bilirubin ≤ twice the institutional upper limit of normal within 21 days of registration on study.

3.1.10.2 Creatinine levels ≤ twice the institutional upper limit of normal within 21 days of registration on study.

3.1.10.3 SGOT must be ≤ 2.5 x the institutional upper limit of normal within 21 days of registration on study.

3.1.11 Negative serum pregnancy test for women of childbearing potential within 14 days of study registration.

3.1.12 Abdominal/pelvic CT scan with contrast and chest CT/x-ray (CT of chest preferred) within 31 days of registration on study. Patients allergic to IV contrast can have MRI of the abdomen/pelvis instead.

3.1.13 Signed study-specific informed consent

3.1.14 Consultation, agreement, and documentation in the patient's chart by a radiation oncologist that patient is suitable to receive radiotherapy per this protocol.

3.1.15 Women of childbearing potential and male participants must practice adequate contraception.

3.1.16 Patients with active HIV infection are eligible if their CD4 count is > 499/cu mm and their viral load is < 50 copies/ml; use of HAART is allowed.

3.2 Conditions for Patient Ineligibility

3.2.1 Patients with non-adenocarcinomas, adenosquamous carcinomas, islet cell (neuroendocrine) tumors, cystadenomas, cystadenocarcinomas, carcinoid tumors, duodenal carcinomas, distal bile duct, and ampullary carcinomas.

3.2.2 Patients managed with a total pancreatectomy, a distal pancreatectomy, or central pancreatectomy.

3.2.3 Prior systemic chemotherapy for pancreas cancer; note that prior chemotherapy for a different cancer is allowable.

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

3.2.5 Previous history of invasive malignancy (except non-melanoma skin cancer) unless the patient has been disease free for at least 2 years prior to study entry (Patients with a previous history of carcinoma *in situ* are eligible.

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 the 3 months of study registration

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 <u>at the time of registration</u>

3.2.7 Pregnant or lactating women

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

3.2.9 If surgical margin status cannot be determined after consultation with the operating surgeon and the institutional pathologist, the patient will be ineligible.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT (5/23/11)

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

4.1 Required Evaluations/Management

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

4.1.1 A tumor tissue block containing normal tissue and peripheral blood must be submitted to this study's central tumor bank for correlative studies prior to treatment (**NOTE**: normal tissue submission is encouraged, but not mandatory).

4.1.2 Glucose and Na, K, Cl, CO_2, BUN within 21 days of study entry

4.2 Highly Recommended Evaluations/Management

4.2.1 Urine specimen prior to protocol therapy.

4.2.2 If the patient consents to participate in the quality of life (QOL) component of the study, sites are required to administer the baseline QOL and functional assessments prior to the start of protocol treatment: FACIT-Fatigue and the PROMIS-derived fatigue short form

5.0 REGISTRATION PROCEDURES

5.1 This study incorporates a two-step registration process and both steps must be completed for all patients.

Step 1 of registration entails web registration as detailed in Section 5.5, at which time the patient will be randomized to either Arm 1 (gemcitabine) or Arm 2 (gemcitabine + erlotinib) as described in the schema.

Step 2 of registration requires a second web registration for all patients.

- Patients that have not progressed and have started the 5th cycle of the first step randomization treatment will then be randomized to either Arm 3 (no radiotherapy) or Arm 4 (radiotherapy with fluoropyrimidine sensitization) as described in the schema.
- If a patient is not going on to the second randomization, step 2 of registration **must** still be completed via web registration.

5.2 General Pre-Registration Requirements

In order to be eligible to enroll patients onto this trial, the center must be credentialed for either 3D-CRT or IMRT. There are two steps in this process for the use of 3D-CRT and an additional step for the use of IMRT.

As a first step in the credentialing procedure, a Facility Questionnaire must be completed by all institutions entering patients on this protocol and/or an SFTP account for digital data submission must be established. The Facility Questionnaire and instructions for establishing the SFTP account are available on the (Image-Guided Therapy Center) ATC web site (http://atc .wustl.edu). The front page of the Questionnaire is for general submission information. Part I of this questionnaire requires the institution to declare if they intend to use 3D-CRT, IMRT or both. This is accomplished by entering 3D-CRT, IMRT or 3D-CRT & IMRT in the appropriate place in Part I., The Facility Questionnaire must be returned to RTOG RTQA Department via FAX at 215-940-8817 or email to rtog-facquest@phila.acr.org. In addition to completing the questionnaire, all institutions must demonstrate their ability to transmit treatment planning data to the ITC (Image-Guided Therapy Center) by performing a "Dry-Run" QA credentialing test. A description of this test can be found on the ATC web site (http://atc.wustl.edu). IMRT credentialing requires a third step of a phantom irradiation (see the next section). Previous credentialing for IMRT with the head & neck PHANTOM will allow institutions to enter patients treated with IMRT on this protocol without additional phantom irradiation.

If an institution has not previously met credentialing requirements for IMRT in the head and neck region (upper aerodigestive tract), an IMRT phantom study with the RPC must be successfully completed. See details below.

RTOG Headquarters will communicate with the registering institution concerning any deficiencies in the Facility Questionnaire and will provide notification when the "Dry Run" test has been successfully completed. RTOG Headquarters will also notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.3 Pre-Registration Requirements for IMRT Treatment Approach

As noted above, in order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "Credentialing Status Inquiry". Instructions for requesting and irradiating this phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG".

The institution or investigator must complete a Facility Questionnaire and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Part I of this questionnaire requires the institution to declare if they intend to use 3D-CRT, IMRT or both. This is accomplished by entering 3D-CRT, IMRT or 3D-CRT & IMRT in the appropriate place in Part I. The Facility Questionnaire must be returned to RTOG Headquarters. Please use front page of Questionnaire for submission information or contact RTOG RTQA Department at 215 574-3219.

Upon review and successful completion of the "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.

5.4 Regulatory Pre-Registration Requirements

5.4.1 **U.S. and Canadian 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, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

5.4.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

5.4.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.4.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.4.3.1 **For institutions that do not have an approved LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx .

5.4.3.2 **For institutions that have an approved LOI for this protocol:**
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.5 Registration

5.5.1 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 web site. 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 Format(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-arrs.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.

5.5.2 EORTC

See Appendix XII (to be provided when this information is available) for additional logistical information for EORTC participating sites (e.g., how EORTC sites will register, how AEs will be reported, how data will be managed, how tissues will be collected and where it will be shipped, etc.).

6.0 RADIATION THERAPY

Arm 3	**No RT**
Arm 4	**RT**

For ARM 4 ONLY: radiation therapy begins after 2nd step registration and post completion of additional gemcitabine or gemcitabine/erlotinib after 2nd randomization. For those patients randomized to ARM 4, radiation therapy should begin not sooner than 7 days or later than 21 days post completion of additional gemcitabine or gemcitabine/erlotinib after 2nd randomization.

Overview of Radiotherapy Process

Be sure to adhere to all of the requirements included in Section 6 in its entirety.

Due to the complexity of this protocol, the following overview is being provided.

Note: All patients must be evaluated by radiation oncology prior to registration and enrollment on this protocol (see Section 3.1)

a. Patients do not receive radiotherapy on this protocol until the completion of the first step systemic therapy (Arm 1 or Arm 2).

b. Only patients who started the 5th cycle of protocol chemotherapy will be allowed to be randomized to Arm 4 and receive radiotherapy on this protocol.

c. After completion of first randomization protocol systemic therapy (Arm 1 or Arm 2), patients are re-imaged and evaluated to confirm the absence of progressive disease. If no progressive disease is found, patients are randomized to receive an additional cycle of protocol chemotherapy +/- radiotherapy (with fluoropyrimidine sensitization: Arm 3 or Arm 4). **CA19-9 levels are not used as an indicator of progressive disease.**

d. Referral to radiotherapy for re-evaluation and treatment planning should be done within 7 days of the 2nd randomization for patients randomized to Arm 4 in order to complete the rapid review process as stated below.

e. TIMELY (within 14 to 21 days after 2nd randomization) digital submission of treatment planning data (CT planning showing relevant targets, isodose lines, complete volumetric data set DVH) to ITC (Image-guided Therapy Center) is mandatory for Arm 4 ONLY.

f. **Patient will not start radiotherapy until the treatment plan is REVIEWED and APPROVED.**

g. Radiotherapy must be administered by either 3D-CRT or IMRT technique.
Please Note: The treating institution must be credentialed for the technique chosen (either 3D or IMRT) see Section 5.

h. Daily IGRT is not required but is permitted.

i. Motion management is not required, but is permitted.

j. This is a one phase RT treatment. There is no "cone down" or "boost" allowed on this study.

6.1 Dose Specifications (3D conformal and IMRT) (5/23/11)

The prescribed dose is 50.4 Gy in 28 fractions of 1.80 Gy. Treatment plans must be normalized such that 90% of the PTV receives 95% of this prescribed dose and 99% of the CTV is to receive 95% of the prescribed dose.

The max and min allowed dose within the PTV are defined in table 6.1:

TABLE 6.1

Prescribed Dose (PD)	Max Dose limit (defined for a point on DVH curve for PTV with a volume of 0.03 cm^3	Max Dose limit (defined for a point on DVH curve for PTV with a volume of 5.0 cm^3	Min Dose limit (defined for a point on DVH curve for the PTV with 98% coverage)
50.4 Gy	**111% of PD = 55.9 Gy**	**105% of PD = 52.9 Gy**	**90% of PD = 45.4 Gy**

Treatment plan normalization must cover 90% of the PTV with 95% of the PD or 47.9 Gy

6.2 Technical Factors

A modern linear accelerator with 100cm SAD and $\geq$ 6MV beam is required. Use of Tomotherapy is allowed.

6.3 Localization, Simulation, and Immobilization (3D Conformal and IMRT) (5/23/11)

6.3.1 Treatment Planning Simulation

Patients will be simulated (and treated) supine with arms up. Immobilization is required. This can range from devices to assist in patient comfort up to alpha cradle or vacuum bag immobilization. Two leveling marks on the each patient's side (2 on the right and 2 on the left) are required.

A dedicated planning CT performed with the patient immobilized on a flat, non-curved, table and in the selected treatment position is required. IV contrast for CT planning is strongly recommended. If IV contrast is not given at the time of simulation, it is necessary to have the images of the contrast enhanced, restaging abdominal CT performed after cycle 5 of chemotherapy readily available (or fused) with the simulation CT in order to permit accurate contouring of the portal vein (PV), celiac axis (CA), and superior mesenteric artery (SMA).

Planning CT scan slice thickness must be no greater than 3 mm.

6.4 Treatment Volumes (3D Conformal and IMRT) (5/23/11)

6.4.1 GTV

By definition there is no GTV within the patient at the time of radiotherapy in this study (GTV has been resected). However, location of the pancreatic tumor prior to resection should be reviewed, noted, and contoured based on the preoperative imaging (please see Section 6.4.2 below).

6.4.2 CTV

Conceptually, this post operative CTV is that area where there is likely to be the highest concentration of residual sub-clinical tumor that can be treated with radiotherapy without resulting in a treatment volume that encompasses an excessive amount of normal organs and normal tissue.

In reviewing the following, please refer to the web based CT atlas which has been created for this purpose at www.rtog.org

In order to approach this process logically, it is necessary to review the surgical and pathological information at the time of treatment planning and the availability of the pre-operative axial imaging is a necessity. Pre and post operative cross-sectional images will be submitted along with the treatment plan. Please see Section 12 for submission link and specifics.

The following should be identified and targeted as specific ROI's.

6.4.2.1 The most proximal 1.0-1.5 cm of the celiac artery(CA) and the most proximal 2.5 to 3.0 cm of the superior mesenteric artery (SMA) CA should include up to the first branching).

6.4.2.2 Those portions of the portal vein (PV) that run slightly to the right of, in front of (anterior) and anteromedial to the inferior vena cava (IVC). These portions are all beneath (caudad to) the bifurcation of the PV into right and left branches as it runs toward the hepatic hilum and continue down to, but do not include, the PV confluence with either the SMV or Splenic Vein (SV). There is substantial anatomical variability from patient to patient with respect to the PV. Cephalad, sometimes the PV bifurcation occurs quite extrahepatically, and sometimes very close to intrahepatically. Similarly, caudally, the PV most often will merge first with the SMV, but may merge with the SV.

The following approach is recommended for contouring the relevant parts of the PV:

- Review the anatomical course of the PV from its cephalad extent to its caudal extent, noting, but not including, the slices where it starts to bifurcate into R and L branches at its cephalad extent and where it starts to join either the SMV or SV caudally.
- Starting from below, contour the PV from just above its junction with the SMV (or SV whichever is more cephalad) and proceed in the cephalad and lateral directions until the PV is directly anterior to the IVC. Continue contouring cephalad and laterally for approximately one to three additional slices (assuming 3 mm slices) until the first slice where the center of the PV width has moved past the right lateral edge of the IVC. Contour the PV on this slice and stop.

6.4.2.3 The preoperative tumor (resected GTV)

6.4.2.4 The pancreaticojejunostomy (PJ); the PJ usually is readily identified by following the pancreatic remnant medially and anteriorly until the junction with the jejunal loop is noted.

6.4.2.5 The aorta from the most cephalad contour of either the celiac axis, PV, or PJ (whichever among these 3 is the most cephalad) to the bottom of the L2 vertebral body. If the GTV contour extends to or below the bottom of L2 then contour the aorta towards the bottom of the L3 vertebral body as needed to cover the region of the preoperative tumor location.

Alternatively, there may be a pancreaticogastrostomy (PG). If there is a PG instead of a PJ, the PG is not included in defining the CTV. Delineating the PG may still be helpful for subsequent reference.

6.4.2.6 Surgical Clips placed for purposes of delineating areas of concern intraoperatively such as close margins, uncinate margin, etc. The significance of surgically placed clips can vary quite a bit and in some cases may be irrelevant for treatment planning purposes. Surgically placed clips should only be included as an ROI if there is documentation in the operative

note or other written documentation from the surgeon of clips placed for a specific tumor related, or planning related purpose.

Steps taken with the above to generate the CTV:

- The celiac axis, SMA and PV ROI's should be expanded by 1.0-1.5 cm in all directions. In most cases, 1.0 cm expansions will be sufficient.
- The aortic ROI should be expanded asymmetrically to include the prevertebral nodal regions from the top of the PJ, PV, or CA (whichever is most superior) to the bottom of L2 (or L3 if GTV location low, see above section). Suggested approximate expansion amounts for the aortic ROI are as follows: 2.5 to 3.0 cm to the right, 1.0 cm to the left, 2.0 to 2.5 cm anteriorly, 0.2 cm posteriorly. The working concept for the lateral margins of this ROI is that one needs to cover the paravertebral nodes laterally but not include either kidney. These expansions will require the use of clinical judgment. Occasionally, the PJ or PV expansion may extend cephalad to above the level of the celiac axis. In that case the aortic expansion should be extended cephalad to the same level as the highest level (CT slice) of the PV or PJ expansion (whichever is more cephalad).
- The PJ should be expanded 0.5-1.0 cm in all directions.
- Delineated clips may be expanded by 0.5 – 1.0 cm in all directions or used without expansion.
- The CTV should then be created by merging the above ROI/ROI expansions (CA, SMA, PV, GTV, Aortic, PJ, , clips) with the following constraints and notes:
    - The posterior margin should follow the contour of the anterior aspect of the vertebral body without actually including more than 0.10 cm of the anterior vertebral body anterior edge.
    - If the PJ cannot be identified, the CTV should be generated without it.
    - If the surgeon has created a pancreaticogastrostomy, do not include it into the CTV.
    - If the CTV with the noted expansions protrudes into a dose limited normal organ such as the liver or stomach, the CTV should be edited to be adjacent (may touch the edge of) the relevant structure.

6.4.3 PTV

The PTV is established by expanding the CTV 0.5 cm in all directions.

6.5 Normal Organ Dose Volume Considerations (3D Conformal and IMRT) (5/23/11)

6.5.1 In addition to the ROI's already discussed, some of which are also normal structures, the normal structures to be contoured are: left and right kidneys, liver, stomach, small intestine, and spinal canal. Contour the kidneys, liver, and stomach in their entireties. Contour the small intestine from the jejunum to 2 cm below the lower extent of the CTV. Contour the spinal canal within the cranial-caudal extent of the CTV and inferiorly/caudally and superiorly/cranially as necessary to identify dose to the spinal cord resulting from either entrance dose or exit dose of any (every relevant) treatment beam.

6.5.2 Normal Tissue Dose-Volume Constraints Per Protocol

Structure	Constraints
Kidney (L & R)	D50% <18Gy (no more than 50% of each kidney can receive more than 18Gy). Mean dose <18Gy. If only one kidney is present, D15% ≤18Gy (no more 15% of the volume of that kidney can receive more than 18 Gy
Liver	Mean liver dose must be ≤ 25 Gy
Stomach and Small intestine	Max dose ≤ 54Gy; D15% < 45Gy (no more than 15% of the organ can receive more than 45Gy)
Spinal canal	Max dose to a point that is 0.03 cm^3 must be ≤ 45Gy

6.6 3D Conformal Beam Arrangements

Beam arrangement selection for 3D conformal treatment will vary based on the shape, size, and location of the CTV and the resulting PTV in relation to normal organs. The following sequences are suggested for consideration roughly in order of increasing complexity. Other approaches are possible. None of these arrangements has to be used exactly as described and appropriate selection of wedges, weighting, and blocking is presumed. Wedges should be considered for use in both axial and sagittal views based on contour variation, other beams, weighting, etc.

6.6.1 Coplanar

6.6.1.1 AP/PA with Right and Left Lateral beams.

6.6.1.2 AP/PA with one or both "laterals" slightly angled anteriorly (5-15 degrees to RAO, LAO). Although this does increase exit beam to the contralateral kidney in each case, the avoidance of entrance beam may result in a dosimetric advantage.

6.6.1.3 RAO (330-350 deg), LAO (10 – 30), Right Lateral, Left Lateral, PA. This complex 5 beam arrangement should be reserved for situations where less complex approaches do not give adequate kidney or other critical normal organ sparing. This approach can be further facilitated by setting the isocenter fairly anteriorly in the CTV. Because of divergence, this minimizes the extent to which the PA field encompasses the kidney parenchyma.

6.6.2 Non-Coplanar

Two laterals or very slightly anteriorly angled beams (one or both) with couch angle of zero. Inferior-Superior beam with couch angle of 90 degrees (or 270 degrees depending on patient orientation) with gantry angle of 20-25 degrees off vertical (warning gantry angles more than 25 degrees off vertical may pose a risk of gantry collision with patient torso), a lightly weighted posterior beam with a couch angle of 0 or a lightly weighted posterior beam with a couch rotation of 90 or 270 degrees and gantry rotation of 5-10 degrees towards opposing the inferior superior beam may be helpful.

6.7 IMRT

6.7.1 Beam Arrangement **(3/4/10)**

Using the International Electrotechnical Commission (IEC) coordinate system, the following beam arrangement is recommended and should be used as a default starting point for linear accelerator based IMRT. This arrangement results in optimal dose distribution in the vast majority of patients. The gantry angles are biased towards the anterior to limit the dose to the kidneys, while the non-coplanar beams limit the dose to the small intestines. Facing the gantry, a 90° couch angle places the patient's feet towards the left of the gantry.

Couch Angle	Gantry Angle
0	350
0	90
0	30
0	310
90	20
90	330

6.8 Field verification

6.8.1 3D Conformal Treatment and IMRT

As a minimum requirement, institutions are required to obtain verification images at the start of treatment and each week thereafter. Prior to the first treatment images that verify the position of the isocenter placement must be obtained. For 3D-CRT this imaging can include individual portal views. Weekly imaging can consist of portal views for 3D-CRT and isocenter verification images. For IMRT orthogonal images verifying isocenter position are required. More frequent (daily) imaging is allowed, but is not required.

6.9 Documentation Requirements

6.9.1 Digital Submission of RT Planning Data

6.9.1.1 **For ARM 4 ONLY: radiation therapy begins after 2nd step registration and post completion of additional gemcitabine or gemcitabine/erlotinib. For those patients randomized to ARM 4, radiation therapy should begin not sooner than 7 days or later**

than 21 days post completion of additional gemcitabine or gemcitabine/erlotinib after 2nd randomization.

The data must be digitally submitted to ITC (Image Guided Therapy Center) within 14 to 21 days from 2nd randomization for review and APPROVAL prior to start of RT. The treatment planning data includes simulation images with isodose lines, structure set, and dose volume histograms. (See Section 12.2 for data submission specifics)

Using the web based systems of the ATC affiliated organizations, all RT plans will be digitally submitted to ITC (Image Guided Therapy Center) for pre treatment review and APPROVAL between 14 to 21 days from 2nd randomization. Review and feedback to institutions will be provided within 3 business days of this submission. Feedback will indicate either that the plan is acceptable as submitted or requires specific modification and resubmission as outlined. RT treatment will not be started until RT plan is APPROVED. Plans requiring modification will be resubmitted within 4 business days for re-review and approval. If a second review is required, approval will be provided within 3 business days.

RT plan submission is recommended as early as possible to avoid delays in RT treatment start. The following table is provided:

FOR ARM 4 ONLY:	Within 14 to 21 business days after 2nd step randomization	Within 3 business days from receipt at ITC	* Within 3-4 business days from RT plan review	* Within 3 business days of resubmission of RT plan
	Submit RT plan digitally to ITC for review	Feedback from review for resubmission of RT plan OR APPROVAL of RT plan	If required, resubmission of RT plan	Feedback from RT review and approval of RT plan: begin RT

* These steps will be repeated if necessary for RT plan approval.

6.9.2 **Treatment Interruptions**

Treatment interruptions should be clearly documented in the patient's medical record. If the sum total exceeds 10 normally scheduled treatment days, the treatment will be considered a deviation unacceptable. 1-4 days of scheduled treatment day interruptions will be considered per protocol. 5-9 days interruption will be considered a variation acceptable.

6.10 Compliance Criteria for Both IMRT and 3D Conformal (5/23/11)

It is anticipated that almost all variations will be eliminated by the prospective review process. Nevertheless, criteria for judging any variations actually treated are provided.

6.10.1 Volume Definitions

6.10.1.1 *Variation Acceptable*

Any variation in contouring of the CTV or PTV which in the opinion of the reviewers does not result in a deviation unacceptable in dose volume coverage of the correct CTV or PTV.

Any variation in the contouring of a normal organ ROI which in the opinion of the reviewers does not result in a deviation unacceptable in dose volume coverage of the correct or actual ROI.

6.10.1.2 *Deviation Unacceptable*

The difficulty that results from an incorrectly delineated CTV, PTV or normal organ ROI relates to whether the dose volume criteria (minimal acceptable coverage) for the correctly delineated CTV, PTV are still respected and for the normal organ ROI's whether the resulting dose volume relationships are felt to represent an unacceptable risk of organ dysfunction.

6.10.2 Per Protocol for Target Structures

6.10.2.1 Doses to PTV and CTV (Per Protocol Limits)

6.10.2.1.1 Acceptable PTV and CTV doses: All plans must be normalized so that 90% of the PTV receives at least 95% of the prescription dose and at least 99% of the CTV receive 95% of the prescribed dose of 50.4 Gy (= 47.9 Gy).

6.10.2.1.2 The Per Protocol statement of the maximum and minimum dose to an additional point that is 5 cm in size falling within the PTV is given in Table 6.1 The following Table 6.2 shows the maximum and minimum dose defining an acceptable deviation from the per protocol limits:

TABLE 6.2 -Variation Acceptabe Dose Limits

Prescribed Dose (PD)	Max Dose limit (defined for a point on DVH curve for PTV with a volume of 0.03 cm^3	Max Dose limit (defined for a point on DVH curve for PTV with a volume of 5.0 cm^3	Min Dose limit (defined for a point on DVH curve for the PTV with 98% coverage)
50.4 Gy	115% of PD = 58.0 Gy	107% of PD = 53.9 Gy	88% of PD = 44.4 Gy

6.10.2.1.3 Deviation Unacceptable: Any deviation worse than the values for the PTV given in table 6.2 above are scored as deviation unacceptable

6.10.3 Organs at Risk Dose Limits

Criticial Structure Variation Acceptable

Structure	Constraints
Kidney (L & R)	D50% ≤ 20Gy (no more than 50% of each kidney can receive more than 20Gy). Mean dose ≤ 20Gy. If only one kidney is present, D15% ≤ 20Gy (no more 15% of the volume of that kidney can receive more than 20 Gy
Liver	Mean liver dose must be ≤ 30 Gy
Stomach and Small intestine	Max dose ≤ 56 Gy; D15% ≤ 50Gy (no more than 15% of the organ can receive more than 50Gy)
Spinal canal	Max dose to a point that is 0.03 cm^3 must be < 50Gy

6.10.4 Deviation Unacceptable: Any Structure doses which do not meet the constraints listed above will be considered a Deviation Unacceptable.

6.11 R.T. Quality Assurance Reviews

Plans requiring modification will be resubmitted within 3 business days for re-review and approval. It is expected that with this process no plan utilized will have worse than acceptable variation and most plans will meet specified requirements for PTV and normal organs and dose maxima.

During this period, radiation treatment plans will be required to be prospectively reviewed by senior RTOG and EORTC radiation oncologists (RTOG: Drs. Ross Abrams and William Regine; EORTC: Drs. Karin Haustermans and Oscar Matzinger).

6.12 Radiation Therapy Adverse Events

See Section 7.8.3.

6.13 Radiation Therapy Adverse Event Reporting

See Sections 7.10 and 7.11 for reporting requirements.

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.

7.1 First Randomization Treatment

7.1.1 Chemotherapy must start within 7 days after registration.

ARM 1

Gemcitabine	1000mg/m^2/week, IV over 30 minutes, once a week for 3 weeks then off 1 week x 5 cycles

ARM 2

Gemcitabine	1000mg/m^2/week, IV over 30 minutes, once a week for 3 weeks then off 1 week x 5 cycles
Erlotinib	100mg/ po/day X 5 cycles until CT/MRI evaluation for progression. Patients without progression will continue erlotinib po daily to second randomization treatment.

7.1.2 Patients must start the 5th cycle of chemotherapy to be eligible for the second randomization. 2nd step registration must be completed for patients with progressive disease by radiographic studies after Arm 1 or Arm 2 treatment is completed; however, these patients will not be randomized to further treatment. Elevation of CA19-9 in the absence of radiographic progression will not be considered disease progression.

7.2 Second Randomization Treatment:

Referral to radiotherapy for re-evaluation and treatment planning should be done within 7 days of the 2nd randomization for patients randomized to Arm 4 in order to complete the rapid review process as stated in Section 6.

7.2.1 Randomization after CT/MRI performed after the 5th cycle of chemotherapy.

7.2.2 Initiation of the 1st cycle of Arm 3 and 4 (6th total cycle of systemic treatment) must occur within 4 weeks of last chemotherapy dose of Arm 1 and 2.

ARM 3

1 cycle identical to the chemotherapy in Arm 1 and 2	(gemcitabine or gemcitabine + erlotinib)

ARM 4

1 cycle identical to the chemotherapy in Arm 1 and 2	(gemcitabine or gemcitabine + erlotinib)
Follow with RT and	To start within 21 days after the last dose of chemotherapy
5FU or Capecitabine	Either 5FU 250mg/m2/day, 7 days per week by a continuous IV infusion via an outpatient infusion pump or capecitabine 825mg/m2/po BID M-F Both starting on day 1 of RT for 5 ½ weeks or until RT completed

7.3 Erlotinib (OSI-774, *Tarceva*) NSC#718781, IND 63383 (5/23/11)

See the Investigator Brochure for comprehensive information (for instructions on obtaining the Investigator Brochure, see Section 7.3.10).

7.3.1 Formulation

Erlotinib is available in 25 mg, 100 mg, and 150 mg white film-coated immediate-release tablets packaged in high-density polyethylene (HDPE) bottle. (A 50 mg tablet is not available.) Each bottle contains 30 tablets. The tablets are round and convex without markings. The 25 mg tablets are 1/4 inches (6 mm); the 100 mg tablets are 11/32 inches (9 mm); and the 150 mg tablets are 13/32 inches (10 mm). OSI-774 excipients include lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

7.3.2 Storage and Stability

Store the intact HDPE bottles at controlled room temperature, not above 25°C (77°F). There is no need to refrigerate the tablets. Current data indicates OSI-774 is stable for at least 3 years at room temperature.

7.3.3 Administration

Erlotinib will be taken as a single daily dose on an empty stomach one hour before or two hours after meals. Prior to starting treatment, the patient will be provided with and instructed in the proper use of a pill diary (see Appendix IX for an example) or a calendar to record their daily pill consumption. This record will be checked for compliance by the investigator. 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**.**

7.3.4 Drug Interactions

Erlotinib is highly protein bound (92% to 95% in humans) and metabolizes primarily via CYP3A4 enzymes. Dose erlotinib cautiously with agents that are highly protein bound or potent CYP3A4 inhibitors/inducers enzymes.

7.3.4.1 *Proton Pump Inhibitor*

Erlotinib's solubility decreases as the pH increases. Co-administration of omeprazole with erlotinib will decrease the AUC and C_{max} by 46% and 61%, respectively.

7.3.4.2 *H_2-antagonist*

Avoid concomitant use of erlotinib with gastric acid reducing agents if possible. When ranitidine 300 mg is given with erlotinib, erlotinib AUC and C_{max} decrease by 33% and 54%, respectively. Increasing the dose of erlotinib will not compensate the loss of exposure. However, if an H_2-antagonist receptor is needed, take erlotinib at least 2 hours before or 10 hours following the H_2-antagonist administration. Dosing such, erlotinib loss of exposure is minimized to AUC of 15% and C_{max} of 17%.

7.3.4.3 *Anticoagulants*

Concomitant NSAIDs, warfarin or warfarin-derivatives may increase bleeding and PT /INR. Dose adjustment may be needed.

Altered coagulation parameters and bleeding have been reported in patients receiving erlotinib alone and in combination with other chemotherapeutic agents and concomitant warfarin-derivative anticoagulants. The mechanism for these alterations is still unknown. When warfarin is co-administered with erlotinib (anytime after Day 5), international normalized ratio (INR), and prothrombin time should be closely monitored and the anticoagulant dose should be adjusted as clinically indicated.

7.3.5 Food-Drug Interaction

Grapefruit juice is a CYP3A4 inhibitor that interferes with the metabolism of erlotinib. Therefore, consumption of grapefruit or grapefruit juice should be avoided during erlotinib treatment.

7.3.6 Smoking

Advise smokers to stop smoking while on erlotinib. Smoking induces CYP1A2 enzymes and alters erlotinib exposure by 64%.

7.3.7 Adverse Events

7.3.7.1 Gastrointestinal Perforation

Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which was observed infrequently. Some cases had a fatal outcome. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease, are at

increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation.

7.3.7.2 Bullous and Exfoliative Skin Disorders

Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions.

7.3.7.3 Ocular Disorders

Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment and are known risk factors for corneal perforation/ulceration. Erlotinib therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

7.3.7.4 Comprehensive Adverse Events and Potential Risks

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Erlotinib (OSI-774, NSC 718781)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 3622 patients.* Below is the CAEPR for Erlotinib (OSI-774).

Version 2.3, March 29, 2010[1]

Adverse Events with Possible Relationship to Erlotinib (OSI-774) (CTCAE 4.0 Term) [n= 3622]			**EXPECTED AEs FOR ADEERS REPORTING** **Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis***
	Dry eye		***Dry eye***
	Eye disorders - Other (eyelash in-growth and/or thickening)		
		Eye disorders - Other (corneal perforation)	
		Keratitis	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
Diarrhea			***Diarrhea***
	Dry mouth		***Dry mouth***
	Dyspepsia		***Dyspepsia***
	Gastrointestinal hemorrhage[2]		
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral***
	Nausea		***Nausea***
Vomiting			***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
HEPATOBILIARY DISORDERS			

		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Skin infection[4]		***Skin infection[4]***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased***
	Blood bilirubin increased		***Blood bilirubin increased***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia***
	Dehydration		***Dehydration***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia***
	Headache		***Headache***
		Intracranial hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough***
	Dyspnea		***Dyspnea***
	Epistaxis		
	Pneumonitis		***Pneumonitis***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia***
	Dry skin		***Dry skin***
		Erythema multiforme	
	Nail loss		***Nail loss***
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus***
	Rash acneiform		***Rash acneiform***
Rash maculo-papular			***Rash maculo-papular***

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

[2]Gastrointestinal hemorrhage could include Colonic hemorrhage, Duodenal hemorrhage, Gastric hemorrhage or hemorrhage of other sites under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation includes Duodenal perforation, Gastric perforation, or perforation in other sites under the GASTROINTESTINAL DISORDERS SOC.

[4]Includes infection of the skin (folliculitis or cellulitis) as complications of rash.

Also reported on erlotinib (OSI-774) trials but with the relationship to erlotinib (OSI-774) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation
EYE DISORDERS - Blurred vision; Eye disorders - Other (orbital cellulitis); Uveitis; Watering eyes
GASTROINTESTINAL DISORDERS - Colitis; Constipation; Duodenal ulcer; Dysphagia; Esophagitis; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (pneumatosis intestinalis); Pancreatitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs
HEPATOBILIARY DISORDERS - Cholecystitis
INVESTIGATIONS - Creatinine increased; INR increased (in patients taking Coumadin); Lymphocyte count decreased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Dizziness; Ischemia cerebrovascular; Peripheral sensory neuropathy
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pharyngolaryngeal pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Urticaria
VASCULAR DISORDERS - Thromboembolic event

Note: Erlotinib (OSI-774) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Note: Erlotinib (OSI-774)-induced diarrhea and/or vomiting has been associated with dehydration, hyperkalemia; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia, increased creatinine, and renal failure.

Note: Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of erlotinib (OSI-774) in patients with baseline hepatic impairment.

7.3.8 Supply

Erlotinib will be supplied free of charge for this study by NCI. PMB/NCI will not be supplying erlotinib to the EORTC sites (see Appendix XII regarding drug supply for EORTC institutions).

7.3.9 Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

7.3.9.1 *Accountability and Supply*

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to the Pharmaceutical Management Branch at (301) 480-4612 or mailing it to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda, MD 20892. For questions about drug orders, transfers, returns, or accountability call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

7.3.10 Investigator Brochure

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator's Brochure (IB). IBs are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by emailing the IB Coordinator (ibcoordinator@mail.nih.gov) or by calling the IB Coordinator at 301-496-5725. Please refer to the Pharmaceutical Management Branch, CTEP, DCTD, NCI "Policy and Guidelines for

Investigational Agent Distribution" at the following link: http://www.rtog.org/ResearchAssociates/QualityControlSiteAudits/PMBPolicy.aspx

7.4 Gemcitabine HCl

See package insert for comprehensive information.

7.4.1 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.

7.4.2 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.

7.4.3 Preparation

Drug vials will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL. The concentration for 200 mg and 1g vials should be no greater than 40 mg/mL.

7.4.4 Administration

An appropriate amount of drug will be prepared with normal saline and administered as a 30-minute intravenous infusion.

7.4.5 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.

7.4.6 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.

7.4.7 Supply

Gemcitabine is commercially available.

7.5 Capecitabine

See package insert for comprehensive information.

7.5.1 Formulation

Capecitabine is supplied as a biconvex, oblong film-coated tablet for oral administration. Only the 500 mg tablets will be utilized in this study. Dosages will be rounded to the nearest 250 mg.

7.5.2 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.

7.5.3 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.

7.5.4 Administration

The capecitabine daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. The tablets should be taken with water. 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 Appendix X for an example) or a calendar to record their daily pill consumption. This record will be checked for compliance by the investigator. 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**.**

7.5.5 Potential Drug Interactions

7.5.5.1 *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.

7.5.5.2 *Oral Anticoagulants*

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

7.5.5.3 *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.

7.5.5.4 *Adverse Events*

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

7.5.5.5 *Storage and Stability*

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

7.5.5.6 *Supply*

Capecitabine is commercially available.

7.6 Fluorouracil (6/8/10)

See package insert for comprehensive information.

7.6.1 Formulation

Each 10 ml ampule contains 500 mg of the drug (50 mg/ml), adjusted to a pH of approximately 9 with sodium hydroxide.

5-Fluorouracil is a fluorinated pyrimidine differing from the normal RNA substrate, uracil, by a fluorinated number 5 carbon. The chemical has a pH of 8.1, and the commercially available solution is buffered with NaOH to obtain an alkaline solution with a pH of around 9.0. The drug is both light sensitive and will precipitate at low temperatures or, occasionally, after a prolonged period at room temperature. Melting range of the solid is 280-284° C. At 25°C the solubility is 1.2 mg/ml in chloroform. The sodium content is 8.24 mg/ml and molecular weight 130.08.

7.6.2 Mechanism of Action

The metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this fashion, 5-FU interferes with the synthesis of DNA. This creates a thymine deficiency that provides unbalanced growth and cell death. Prolonged administration of 5-FU continuous infusion may favor 5-FU incorporation into RNA.

7.6.3 Pharmacokinetics

5-FU is rapidly absorbed by the tissues. Studies with radioactively labeled 5-FU administered i.v., have indicated passage of the drug through the blood-brain barrier. Intravenous administration gives a half-time of 5-7.5 minutes at a 15 mg/kg dose. Following the i.v. administration of a single 15 mg/kg dose of radioactively labeled drug, levels of 28 mcg/ml, 2-8 mcg/ml, and 0.72 mcg/ml in plasma were observed at 10 minutes, 2 hours, and 24 hours, respectively. The drug is largely catabolized in the liver and excreted in the form of nontoxic metabolites. Eighty percent of the drug is excreted as CO_2 from the lungs, and approximately 15% is excreted intact in the urine in 6 hours. Of this, 90% is excreted in the first hour.

7.6.4 Administration

5-FU will be administered as a continuous IV infusion at a dose of 250 mg/m^2/day beginning on day #1 of radiation and ending on the last day of radiation treatment.

7.6.5 Known Side Effects and Toxicities

Mild nausea and vomiting, stomatitis, anorexia, diarrhea, alopecia, hand/foot syndrome, myelosuppression, cerebellar ataxia, skin, and cardiac toxicity have been observed. The most common toxicities with continuous infusion 5-FU are mucositis and hand/foot syndrome.

7.6.6 Storage and Stability

5-FU is stored at room temperature. 5-FU is light sensitive and forms precipitates at low temperatures.

7.6.7 Supply

Commercially available.

7.7 Non-Canadian International Institutions:

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.8 Dose Modifications (5/23/11)

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 7.10).

General considerations:

- For patients on gemcitabine and erlotinib, if either drug is permanently stopped for toxicity the patient may continue with the other agent alone.
- For gemcitabine related toxicities resulting in holding the dose of gemcitabine, erlotinib will not be omitted.
- For erlotinib related toxicities resulting in holding administration of erlotinib gemcitabine will not be omitted.
- Missed doses are to be omitted rather than made up.

7.8.1 Dose Modifications for Gemcitabine

7.8.1.2 *Dose Levels*

Dose Levels	
Full dose	1,000 mg/m^2
Dose level -1	750 mg/m^2
Dose level -2*	500 mg/m^2

* Patients who require more than two permanent dose reductions will be removed permanently from gemcitabine treatment.

7.8.1.3 *Hematologic Toxicities*

For Day 1 of each cycle, patients must have an ANC ≥ 1,500 x 10^6/L AND platelets ≥ 100,000 x 10^6/L before receiving treatment with gemcitabine. If counts are less than this, then treatment must be delayed. If blood counts still do not meet these requirements after 4 weeks, the patient will be removed from all protocol treatment.

On Day 1 of the first cycle, patients will receive gemcitabine at a dose of 1,000 mg/m^2.

On Days 8 and 15 of each cycle the dose of gemcitabine to be given will depend on the patient's blood counts on that day according to the following table.

If patients had a non-permanent dose reduction on day 15 and their ANC ≥1,500 and platelets are ≥100,000 by day 1 of the next cycle, they will return to full dose(the dose prior to the non-permanent dose reduction).

Toxicity on Day 8

ANC: Day 8	PLATELET: Day 8	DOSE MODIFICATION
≥1,000 AND	≥100,000	No dose modification
750-999 and	≥75,000	Decrease by 1 dose level. This dose reduction is not permanent
≥1,000 and	75,000-99,999	Decrease by 1 dose level. This dose reduction is not permanent
500-749 or	20,000-75,000	Omit gemcitabine and reduce by 1 dose level on day 15. This dose level is not permanent
<500 or	<20,000	Omit gemcitabine and reduce by 1 dose level on Day 15. This dose reduction is permanent

Toxicity on Day 15

ANC: Day 15	PLATELET: Day 15	DOSE MODIFICATION
≥750 AND	≥75,000	If day 8 ANC was ≥ 1,000 and platelet count was ≥ 75,000 then the day #15 gemcitabine dose is the same as day 8. If day 8 ANC was 750-999 and the platelet count was > 75,000 then the day #15 gemcitabine dose is the same as day 8. If day 8 ANC was 500-750 or Platelet 20,000-75,000 then the day #15 gemcitabine dose is 1 dose level reduced from the day 1 dose. This reduction is not permanent. If day 8 ANC < 500 or platelet < 20,0000 then the day #15 gemcitabine dose is 1 dose level reduced from the day 1 dose. This dose reduction is permanent.
500-749 and	≥75,000	If day 8 ANC was ≥ 1,000 and platelet count was ≥ 75,000 then the day #15 gemcitabine dose is 1 dose level reduced from the day 8 dose. This dose reduction is not permanent. If day 8 ANC was 750-999 and the platelet count was > 75,000 then the day #15 gemcitabine dose is the same as the day 8 dose. If day 8 ANC was 500-750 or Platelet 20,000-75,000 then the day #15 gemcitabine dose is 1

		dose level reduced from the day 1 dose. This reduction is not permanent. If day 8 ANC < 500 or platelet < 20,0000 then the day #15 gemcitabine dose is 1 dose level reduced from the day 1 dose. This dose reduction is permanent.
≥500 and	50,000-74,999	If day 8 ANC was ≥ 1,000 and platelet count was ≥ 75,000 then the day #15 gemcitabine dose is 1 dose level reduced from the day 8 dose. This dose reduction is not permanent. If day 8 ANC was 750-999 and the platelet count was > 75,000 then the day #15 gemcitabine dose is the same as the day 8 dose. If day 8 ANC was 500-750 or Platelet 20,000-75,000 then the day #15 gemcitabine dose is 1 dose level reduced from the day 1 dose. This reduction is not permanent. If day 8 ANC < 500 or platelet < 20,0000 then the day #15 gemcitabine dose is 1 dose level reduced from the day 1 dose. This dose reduction is permanent.
<500 or	<50,000	Omit gemcitabine. If the dose of gemcitabine was also omitted on Day 8, then reduce the dose of gemcitabine on Day 1 of the following cycle by 1 dose level. This dose reduction is permanent.

7.8.1.4 *Non-Hematologic Toxicities Related to Gemcitabine*

Grade	Dose Modifications
0-2	Full dose
3-4	Hold until resolution to ≤ Grade 2, then decrease by 1 dose level from current dose. If toxicity does not resolve within 4 weeks, discontinue gemcitabine treatment.

Grade 3/4 nausea or vomiting only requires dose modifications if it persists > 24 hours despite adequate antiemetic medication. There are no dose modifications for alopecia.

Grade 3/4 adverse events not related to treatment such as a thrombosis, pulmonary embolus or non-neutropenic infection do not require dose reductions when treatment is resumed.

For suspected > grade 2 pneumonitis consult with a medical oncology co-principle investigator.

Non-hematologic toxicities thought by the treating investigator to be due to erlotinib, as described in Section 7.8.2 do not require dose modification of gemcitabine.

7.8.2 Dose Modifications for Erlotinib

7.8.2.1 *Dose Levels*

Full dose	100 mg/day
Dose level -1	75 mg/day
Dose level -2*	50 mg/day

* Patients who require more than two dose reductions will be removed permanently from erlotinib treatment.

7.8.2.2 *Dose Modification Guidelines Table – Erlotinib*

Toxicity	Grade	Erlotinib dosage modification	Guideline for management
Keratitis	1	None	No intervention
	2 (if ≤ 14 days)	None**	Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks
	2 (if >14 days)	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level	
	≥ 3	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level	
Diarrhea	1	None	No intervention
	2	None **	Loperamide (4 mg at first onset, followed by 2 mg every 2–4 hrs until diarrhea free for 12 hrs)
	≥ 3 (*despite optimal use of loperamide)*	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level	
Rash	1	None	No intervention
	2	None **	Any of the following: minocycline+, topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)
	≥ 3	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level	
Bilirubin	≥3 x ULN	Hold until grade ≤2 And then Reduce 1 dose level	
Liver transaminase	≥ 5 x ULN	Hold until grade ≤2 And then Reduce 1 dose level	
Signs and symptoms of Interstitial Pneumonitis		Hold pending diagnosis Permanently discontinue if diagnosis is confirmed and considered possibly related to OSI-774	Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated.
Other toxicity	≥ 2 prolonged clinically significant toxicity	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level*	Treatment as appropriate
**if dose has been previously held for grade 2 rash or diarrhea, and grade 2 symptoms recur, OR if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce dose one level +recommended dose: 200mg po bid (loading dose), followed by 100mg po bid for 7-10 days			

7.8.2.3 *Additional Information for Erlotinib*

- GI perforation: In the event of bowel perforation, patient should be removed from erlotinib therapy.
- Ocular AEs: Erlotinib should be interrupted for acute/worsening eye pain and should be discontinued in patients with persistent inflammation or severe eye surface damage.

7.8.3 Dose Modifications for Fluorouracil or Capecitabine and Radiation

7.8.3.1 *Hematologic Toxicity*

Parameter	Treatment	Dose Modification
ANC > 1000 **and** platelets > 75,000	Fluorouracil Capecitabine	No dose modification
ANC 500-999 **and/or** platelets 50,000-75,000	Fluorouracil Capecitabine Radiation	Continue radiation. Hold fluorouracil or capecitabine until ANC > 1000 and platelets > 75,000, then resume at permanent 25% dose reduction.
ANC < 500 **and/or** Platelets < 50,000	Fluorouracil Capecitabine Radiation	Hold fluorouracil or capecitabine and radiation until ANC > 1000 and platelets > 75,000 then resume radiation and restart fluorouracil or capecitabine at permanent 25% dose reduction.
NOTE: Patients who have required two dose reductions and who experience a third episode of ANC < 1000 and platelets < 75,000 will complete radiation and but will not receive additional fluorouracil		

7.8.3.2 *Non-Hematologic Toxicity*

Only toxicities related to treatment require dose modifications. For patients experienced adverse events unrelated to treatment (such as deep venous thrombosis, pulmonary embolus or non-neutropenic infection), when treatment is resumed after recovery from these adverse events, no dose modifications are required.

Parameters	Treatment	Dose Modification
Grade 3 or 4 AE, 1st occurrence	Fluorouracil Capecitabine Radiation	Hold fluorouracil or capecitabine and radiation until toxicity has resolved to ≤ grade 2, then resume radiation and fluorouracil or capecitabine with a permanent 25% dose reduction
Grade 3 or 4 AE, 2nd occurrence	Fluorouracil Capecitabine Radiation	Hold fluorouracil or capecitabine and radiation until toxicity has resolved to ≤ grade 2, then resume radiation and fluorouracil or capecitabine with a permanent 25% dose reduction
Grade 3 or 4 AE, 3rd occurrence	Fluorouracil Capecitabine Radiation	Hold fluorouracil or capecitabine and radiation until toxicity has resolved to ≤ grade 2, then resume radiation and fluorouracil or capecitabine with a permanent 25% dose reduction
Grade 3 or 4 AE, 4th occurrence or Grade 3 or 4 AE that persists for > 4weeks	Fluorouracil Capecitabine Radiation	Discontinue fluorouracil or capecitabine and radiation permanently
Grade 2 Hand/Foot Syndrome	Capecitabine	Hold until resolves to ≤ grade 1, then resume at permanent 25% dose reduction
Grade 3 Hand/Foot Syndrome	Capecitabine	Hold until resolves to ≤ grade 1, then resume at permanent 50% dose reduction

7.9 Modality Review

The medical oncology co-chairs will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. Drs. Safran, Philip, and Moore will perform chemotherapy reviews. 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/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The medical oncology co-chairs will perform a Quality Assurance Review after complete data for the first 50 cases enrolled has been received at RTOG Headquarters. The medical oncology co-chairs will perform the next review after complete data for each of the next 100 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first. Medical oncology reviews need to be completed prior to presenting/publishing the primary endpoint results.

7.10 Adverse Events (5/23/11)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. 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 located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

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

7.10.1 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 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.

7.10.2 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 drug 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 in the offspring of a patient who received protocol treatment.

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 both the NCI at 301-230-0159 and 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. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. **Note:** Sites must 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.

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site.

7.10.3 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.

7.11 AdEERS Expedited Reporting Requirements (6/8/10)

CTEP defines expedited AE reporting requirements for phase 2 and 3 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 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agent (Erlotinib) in this Study.

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unex-pected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

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

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

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

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

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

Exceptions to AdEERS Reporting: These events are common and known to be associated the protocol regimen, and should not require expedited reporting (in addition to routine reporting through case report forms).

a) Grade 3 N/V/D without or with hospitalization; and

b) G3-4 myelosuppression with or without hospitalization.

7.12 CRADA

NCI/DCTD Standard Language for an Agent Covered by a Collaborative Agreement with NCI

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

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

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

8.0 SURGERY

8.1 Surgical Quality Assurance Reviews

A full surgical quality assurance review is required for this study. The review will be performed by the Surgical Oncology Co-Chair, Adam Berger, M.D., after complete data for 50 cases have been received at RTOG Headquarters. Dr. Berger will then perform the next reviews on a quarterly basis when complete data has been received at RTOG Headquarters.

8.2 General Considerations

In resected pancreatic cancer, the presence of gross or microscopic tumor at the surgical margin has been associated with poor survival following pancreaticoduodenectomy. Of particular concern is the fact that few studies, including most randomized controlled trials have failed to require precise documentation of margin status or information as to how the pathologic margins were assessed. Given that adjuvant therapy, chemoradiation in particular is designed to impact the risk of local recurrence and that such therapies are less effective in the presence of positive margins, the omission of information about surgical margin status makes interpretation of treatment efficacy extremely difficult. For the current study, documentation of surgical margins will be mandatory. Only patients with negative microscopic margins (R0) or those with gross negative and microscopically positive margins (R1) will be enrolled. R0 versus R1 status will serve as a stratification criterion.

In pancreaticoduodenectomy, there are three surgical margins of interest; 1) the common bile duct, 2) the pancreatic parenchymal margin and 3) the retroperitoneal margin- or that soft tissue abutting the proximal 3-4 cm of the superior mesenteric artery (SMA). It is the status of the retroperitoneal margin that is often poorly documented both by the operating surgeon and pathologist alike and it is the most commonly positive margin following pancreaticoduodenectomy. Only the operating surgeon can differentiate the difference between an R1 and an R2 resection as the pathologist cannot determine if gross disease has been left attached to the SMA. Therefore, for trial inclusion, it is required that the operating surgeon document the presence or absence of gross disease at the SMA. This should be documented either as part of the operative note or within the RTOG 0848 Surgery Document. Finally, statement of the status of all three surgical margins be specifically detailed in the pathology report.

8.2.1 Specific Requirements

Either classic (Whipple) or pylorus-preserving pancreaticoduodenectomy should be performed. The retroperitoneal dissection along the medial edge of the uncinate process and the right lateral border of the superior mesenteric artery (SMA) is an important oncologic portion of

pancreaticoduodenectomy. All soft tissue to the right of the SMA should be removed (and documented in the operative report). This requires exposure and dissection along the right lateral border of the SMA.

8.3 Resection Classification and Operative Note Dictation

The attending surgeon should have dictated the operative note and complete the RTOG 0848 Surgery Document (Appendix V). The surgical form should be filled out in conjunction with the operating surgeon in order to document the status of the margins and whether there was any gross residual disease.

Ideally, the operative report should contain:

- A section describing the operative findings including the site and anatomy of the primary tumor.
- A statement as to whether or not the surgeon believes there is macroscopic residual tumor.

Ideally, the results of the final microscopic surgical margins from the finalized pathology report should be incorporated into the final dictated and edited operative report.

The definitions for the resection classification that should be utilized in operative notes include:

- R0: macroscopically complete removal with negative microscopic margins (bile duct, pancreatic parenchyma, and SMA margins).
- R1: macroscopically complete removal with any microscopically positive surgical margin (bile duct, pancreatic parenchyma, or SMA margins).
- R2: macroscopically incomplete tumor removal with known or suspected gross residual disease.

8.4 Surgical Pathology

If resection (R status) and margin status cannot be determined from the operative dictation or the pathology report, the patient will be ineligible for this protocol.

8.4.1 Pathology Review

8.4.1.1 Local Pathology Review of the Resected Pancreatic Tumor

Pathologic examination of the resected pancreatic tumor specimen should be carried out by a local surgical pathologist with experience in the diagnosis of pancreatic adenocarcinoma.

All relevant margins (SMA, pancreatic, and bile duct) should be identified and inked by the surgeon and pathologist at the time of specimen removal. Any segment of a resected vessel should also be identified and marked. The SMA margin should be separately inked according to the procedures as set out in the 6th edition of the AJCC staging system and the College of American Pathologists (CAPS) guidelines for reporting of resected exocrine pancreatic cancer (2005—see Appendix V).

8.4.1.2 Final Pathology Report

The pathology report must contain all of the elements as outlined in the CAPS guidelines (Appendix V). In particular, there should be comment on the following:

- Final margin status for the bile duct, pancreatic parenchymal, and SMA margin;
- Tumor size;
- Degree of differentiation (poor, moderate, well);
- Number of lymph nodes examined;
- Number of positive lymph nodes;
- Local invasion;
- Extent of involvement of named vessel(s) if present.

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. These may include anti-emetics, anti-diarrheals, red packed cells, platelets, pancreatic enzymes, nutritional supplements, and drugs

given topically or systemically for the treatment of cutaneous toxicities of erlotinib. Myeloid growth factors are allowed for the treatment of neutropenia.

9.1.1 Proton Pump Inhibitor

Erlotinib's solubility decreases as the pH increases. Co-administration of omeprazole with erlotinib will increase the AUC and C_{max} by 46% and 61%, respectively.

9.1.2 H_2-antagonist

Avoid concomitant use of erlotinib with gastric acid reducing agents if possible. When ranitidine 300 mg is given with erlotinib, erlotinib AUC and C_{max} decrease by 33% and 54%, respectively. Increasing the dose of erlotinib will not compensate the loss of exposure. However, if an H_2-antagonist receptor is needed, take erlotinib at least 2 hours before or 10 hours following the H_2-antagonist administration. Dosing such, erlotinib loss of exposure is minimized to AUC of 15% and C_{max} of 17%.

9.1.3 Patients are recommended to wear sun screen protection, hat, long sleeves to avoid sun as it can exacerbate skin rash.

9.1.4 Patients should be informed that skin toxicity is to be expected during treatment with erlotinib. Skin toxicity may take the form of dry skin, rash, acneiform eruption, or hair or nail changes. Prophylactic treatment of the skin may prevent or reduce skin toxicity. The patient should be encouraged to use an alcohol-free, emollient cream applied twice a day to the entire body as soon as the patient starts therapy with erlotinib. Creams and ointments are recommended because they have a greater ability to retain moisture than lotions. Examples of suitable emollient creams include: Neutrogena® Norwegian formula, SARNA® Ultra, Vanicream™, Aveeno® (fragrance-free formulation), and Eucerin® cream. Other over-the-counter aqueous creams or emulsifying ointments may also provide symptomatic benefit. Lotions should be avoided because they often contain alcohol, which will dry the skin. Patients should also be encouraged to use a titanium dioxide or zinc oxide-based sunscreen product applied to sun-exposed areas twice per day.

9.2 Non-permitted Supportive Therapy

Erythroid growth factors are discouraged due to thrombotic potential.

10.0 TISSUE/SPECIMEN SUBMISSION (5/23/11)

10.1 General Information

Tumor block, containing normal tissue submission and peripheral blood submission are mandatory at study entry. (**NOTE**: Normal tissue is not mandatory but is encouraged). Urine submission at study entry is highly recommended. These specimens are to be submitted to the RTOG Biospecimen Resource for correlative studies. In addition, at the time of progression, this study encourages the submission of peripheral blood and tumor tissue (if a biopsy is performed to document progression).

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 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.

10.2 Specimen Collection

Samples are required from all patients as part of eligibility criteria. Patients without a tumor tissue block and peripheral blood submission are ineligible for the study.

Specimens are to be collected at baseline in all eligible patients. These include the tumor tissue block and peripheral blood (plasma and whole blood). The tumor tissue block will be derived from the material removed at the time of surgery and preserved in formalin. Snap freezing is not necessary, as tissue submitted will be those preserved in formalin.

Highly Recommended: Urine at baseline. At the time of progression, if a biopsy is obtained to document progression, it is highly recommended that a block of the tumor tissue be sent to the

RTOG Biospecimen Resource. In addition peripheral blood (10 cc) is also requested at the time of progression.

10.2.1 Tissue Blocks

The following must be provided in order for the case to be evaluable for the Biospecimen Resource (Required):

10.2.1.1 One H&E stained slide

10.2.1.2 A paraffin-embedded tissue block of the primary tumor containing normal tissue (**NOTE:** normal tissue submission is not mandatory but is encouraged).
If the institution is not able to release the block, a 5 mm diameter core of tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled "tumor" with the surgical pathology number, as well as 25 unstained sections on plus slides that are to be cut at 5 microns taken from the block after it has been punched. NOTE: A kit with the punch tool, specimen tube, and instructions can be obtained free of charge from the Biospecimen Resource. To request a kit, contact the Biospecimen Resource at RTOG@ucsf.edu or 415-476-RTOG (7864). Block or core must be clearly labeled with the pathology identification number that corresponds to the submitted Pathology Report.
See Appendix VI for specimen punch tool kit and instructions.

10.2.1.3 A Pathology Report documenting that the submitted block or core contains tumor and the clinical status. 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 report 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; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's RTOG case number.

10.2.2 Whole Blood, Plasma, and Urine

10.2.2.1 5 cc of whole blood, and 7-10cc of blood to be separated for plasma are required.
See Appendix VII for blood collection kit, processing and shipping instructions.

10.2.2.2 10-25 mL urine to be collected at study entry.
See Appendix VIII for urine collection kit, processing and shipping instructions.

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 whole blood, plasma, and urine; the RTOG protocol number, the patient's RTOG case number, and method of storage, for example, stored at -80° C, must be included.

10.2.2.4 To request a kit, contact the Biospecimen Resource at **RTOG@ucsf.edu or 415-476-RTOG (7864)**.

10.3 Storage Conditions (6/8/10)

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 (ship out 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.

10.4 Specimen Collection Summary (5/23/11)

Mandatory Specimens			
Specimens taken from patient:	Collected When:	Submitted As:	Shipped:
1 block primary tumor containing normal tissue **(NOTE**: normal tissue is not mandatory but is encouraged) OR 5mm	Removed at time of surgery	Preserved in formalin; paraffin embedded	Ambient

punch of tumor tissue block with 25 unstained sections on plus slides.			
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Prior to treatment	Frozen plasma samples containing of 0.5 mL per aliquot in 1 mL cryovials (five to ten) Store frozen at -80°C	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 , (purple/lavender top tube) and mix	Prior to treatment.	Frozen whole blood samples containing of 1 mL per aliquot in 1 mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier

Highly Recommended Specimens			
Specimens taken from patient:	Collected When:	Submitted as:	Shipped:
10-25 mL clean-catch urine	At study entry	Two 5-10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20° or 80° C	Urine sent frozen on dry ice via overnight carrier
1 block progression tumor OR punch of block plus 25 unstained sections on plus slides.	Disease progression	Preserved in formalin; paraffin embedded	See Appendix VI
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Disease progression	Frozen plasma samples containing of 0.5 mL per aliquot in 1 mL cryovials (five-ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube#2, (purple/lavender top) and mix	Disease progression	Frozen whole blood samples containing 1.0 mL per aliquot in 1 mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier

10.5 Submit materials as follows: (4/12/12)

Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94115

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, 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 per case for the protocol specified materials submitted to the Biospecimen Resource at the University of California San Francisco. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.7 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

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. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.8 Correlative Science

The following assays will be performed on the paraffin-embedded material. Additional targets may be included in the future with the involvement of additional investigators.

10.8.1 Immunohistochemistry

1. E-Cadherin, vimentin
2. C-Met, RON
3. EGFR, phosphor-EGFR, IL-1, NFkB, EGF, amphiregulin, heregulin, p-MAPK, phospho-AKT
4. Notch1, shh

10.8.2 Quantitative RT-PCR

Ribonucleotide reductase M1 subunit, HGF, HGFL

10.8.3 K-Ras mutational status

10.8.4 EGFR by FISH

10.9 Steering Committee for the Allotment of Tissue

A steering committee will be formed to provide scientific review of requests for tissue from this international study after protocol specified studies are complete and the primary results of the study have been reported.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.2 Evaluation for Progression following First Randomization

Patients must be evaluated for progression by IV contrast CT (or MRI, if allergic), and start 2nd step systemic treatment within 4 weeks of completing step 1 systemic treatment. CA19-9 levels are not used as an indicator of progressive disease.

11.3 Quality of Life Assessments

Patients should complete the FACIT-Fatigue and the PROMIS-derived fatigue short form at baseline before systemic therapy initiation, after completion of Arm I or 2 systemic therapy but prior to clinical evaluation for progression, as well as at 9, 12, and 24 months from start of Arm 1 or 2 therapy.

FACIT-Fatigue, version 4, is a 13-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue (SB Yellen, 1997). A 5-point intensity type of rating scale (from "not at all" to "very much") is used. The FACIT-Fatigue is a psychometrically sound instrument and has been widely used to measure fatigue for patients with various chronic illnesses including cancer and pancreatic cancer (SB Yellen, 1997; DW Robinson, 2008). This questionnaire can be completed by patients in approximately 5 minutes. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they

can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. Note: The FACIT-Fatigue has been translated into 49 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at http://www.facit.org/translation/licensure.aspx.

PROMIS-fatigue, A Novel Short Form Fatigue Scale is a 7-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. This questionnaire was developed to minimize patient burden and for ease of use in oncology populations. While the psychometric properties of this 7-question short fatigue scale have been validated in the general population (SF Garcia, 2007; J-S Lai, 2008), validation in patients with cancer is underway. A "cross-walk" has been successfully developed between the PROMIS fatigue item bank and the PROMIS-Cancer fatigue item bank that produced the short form measure. These two item banks, sharing 54 common items, were linked by equating item parameters using items that held stable psychometric properties between the cancer and general population populations in which they were tested. Results showed that cancer patients reported more severe fatigue (1/3 standard deviation more severe, but the same scale characteristic curve slope) than the general population, which matches clinical expectations (D Cella, 2007). This questionnaire can be completed by patients in less than 5 minutes. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. Note: The PROMIS-fatigue is available in validated English and Spanish language formats, and is currently being translated into German and Dutch; is accessible through the PROMIS Assessment Center website: http://www.assessmentcenter.net/ac1/.

11.4 Criteria for Discontinuation of Protocol Treatment

- Progression of disease;
- A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0.

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

Item	Due
Demographic Form **(A5)**	**Within 2 weeks of 1st step registration**
Initial Evaluation Form **(I1)**	
Slides/Blocks **(P2)** [For studies with pathology]	
Surgery Form**(S1)**	
Surgical Operative Report**(S2)**	
Surgical Pathology Report**(S5)**	
Specimen Transmittal Form**(ST)**	
FACIT-Fatigue QOL(FA)	
PROMIS Fatigue QOL **(PR)**	
FACIT-Fatigue QOL(FA)	
PROMIS Fatigue QOL **(PR)**	After completion of Arm I or 2 systemic therapy but prior to clinical evaluation for progression, and then at 9, 12, and 24 months from the START OF ARM 1 OR 2 therapy
Post Arm 1 or 2 tumor status form **(F3)**	1 week after evaluation for disease progress post arm 1 or 2 treatment
Arm 1 or 2 Treatment Form **(TF)**	1 week after completion of Arm 1 or 2 treatment
Arm 3 or 4 1st cycle Treatment Form **(AT)**	1 week after completion of 1st cycle Arm 3 or 4 treatment
Arm 4 Concurrent Treatment Form **(SF)**	1 week after completion of concurrent Arm 4 treatment (chemo/RT)
Preoperative cross-sectional images (access http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx for submission specifics)	1 week after completion of RT Arm 4 treatment
Follow-up Form **(F1)**	Every 6mo x 2 then annually
FOR PATIENTS WHO DO NOT RECEIVE ARM 3 OR 4 TREATMENT	
FOR PATIENTS WHO DO RECEIVE ARM 3 OR 4 TREATMENT	Every 3mo x 2 yrs then every 6mo x 3yrs then annually(from the start of arm 1 or 2 treatment)

***NOTE:** Copies of simulation and port films and the complete RT daily treatment record for the (site) will be submitted to RTOG Headquarters ONLY if specifically requested.

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) ARM 4 ONLY (5/23/11)

Item	Due
Preliminary Dosimetry Information (DD) †Digital Data Submission – Treatment Plan along with pre and post operative CT scans submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following **and must be submitted for plan approval pre-RT start:** • CT data, contours for critical normal structures, all GTV, CTV, and PTV contours • Digital beam geometry for RT fields • Dose distribution • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan Digital Data Submission Information Form **(DDSI)** – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/ddsi/ddsi.html) Hard copy isodose distributions for total dose plan **(T6)** **NOTE: Sites must notify ITC via e-mail (itc@ wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, "dry run" or "benchmark".**	Within 7-14 days post 1st chemo cycle after 2nd randomization
Final Dosimetry Information Radiotherapy Form **(T1) [copy to HQ and ITC]** Daily Treatment Record **(T5) [copy to HQ and ITC]** Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	Within 1 week of RT end

†Available on the ATC web site, http://atc.wustl.edu/

NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

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 Endpoint(s)

13.1.1 Primary Endpoints

13.1.1.1 For the erlotinib question (first randomization): Overall survival (OS) (failure: death due to any cause)

13.1.1.2 For the chemoradiation question (second randomization): Overall survival (OS) (failure: death due to any cause)

13.1.2 Secondary Endpoints

For both the erlotinib question (first randomization) and the chemoradiation question (second randomization) unless otherwise noted

13.1.2.1 Disease-free survival (failure: local or regional disease progression, distant metastases, second primary, or death due to any cause)

13.1.2.2 Adverse events

13.1.2.3 Pre-op imaging to determine frequency of objective criteria of resectability

13.1.2.4 Quality of Life: fatigue as measured by the FACIT-F (primary) and the PROMIS derived short form (exploratory)

13.1.2.5 Laboratory correlative studies related to K-Ras (first randomization only), see section 13.5

13.2 Stratification

Prior to the first randomization, patients will be stratified with respect to the following stratification variables: nodal status (involved vs. uninvolved), serum CA19-9 (≤ 90 vs. > 90-180), and surgical margins (positive vs. negative). Prior to the second randomization, patients will be stratified with respect to the following stratification variable: first treatment (gemcitabine vs. gemcitabine + erlotinib). Patients must start the 5th cycle of chemotherapy to be eligible for the second randomization. The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.[Zelen, 1974]

13.3 Sample Size and Power Justification

13.3.1 The sample size calculation for this trial begins with the primary endpoint question in the second randomization and the corresponding hypothesis that the use of concurrent fluoropyrimidine and radiotherapy following adjuvant gemcitabine based chemotherapy improves overall survival for patients who are without evidence of progressive disease after 5 cycles of gemcitabine based chemotherapy. The primary endpoint of overall survival for patients who do not progress after adjuvant chemotherapy will be measured from the date of the second randomization (chemotherapy vs. chemotherapy followed by chemoradiation) to the date of death. However, by the time these patients are randomized to the chemoradiation question, they will already have been on the trial for approximately 6 months. The median survival time (MST) for the gemcitabine alone arm from the CONKO-1 trial [Neuhaus, 2008] was 22 months from study entry. Since patients randomized to the chemoradiation question will be those who did not progress following adjuvant chemotherapy, it is projected that the control arm will have a MST of 23 months from study entry. Adjusting for the 6 months that patients will have already been on trial, the sample size for the primary hypothesis for the second randomization (i.e., that chemotherapy followed by chemoradiation will improve overall survival for patients who are disease free following adjuvant chemotherapy) will be based on improving MST from 17 months to 22.5 months.

The required sample size for the primary endpoint of overall survival for the chemoradiation question is based on the following conditions:

- Survival times are exponentially distributed with (at least approximately) proportional hazards between the chemotherapy and chemoradiation treatment arms
- The control arm will have a MST of 17 months from the second randomization (monthly hazard of 0.0408)
- The experimental arm will have a MST of 22.5 months from the second randomization (monthly hazard of 0.0308)
- One-sided test at $\alpha = 0.05$
- 90% power

- 5 years of accrual with 3 years of follow-up
- Three interim significance tests and a final test are planned

Using the group sequential design method [Pocock, 1977] with 3 interim analyses, 640 eligible patients are required to detect an increase in MST from 17 to 22.5 months [measured from the date of second randomization (chemotherapy vs. chemotherapy followed by chemoradiation) to the date of death], translating into a hazard ratio (experimental/control) of 0.76. It is projected that up to 25% of patients entering the first randomization will not proceed to the second randomization due to progression, death without progression, did not start the 5th cycle of adjuvant chemotherapy treatment, or refusal. Adjusting for these factors and for an ineligibility or lack-of-data rate of up to 10%, the final targeted accrual for this study will be 950 patients.

13.3.2 The primary hypothesis for the first randomization is that the addition of erlotinib to standard adjuvant gemcitabine will increase overall survival for patients with resected head of the pancreas adenocarcinoma. A total of 950 patients will be entered onto this trial to answer the chemoradiation hypothesis (per Section13.1.1.1). As it is assumed that up to 10% of patients will not be evaluable due to ineligibility or lack-of-data, there will be 856 evaluable patients for the erlotinib question. There is some uncertainty as to whether the traditional proportional hazards assumption will be met or if the benefit of erlotinib will increase over time. Design information follows for both situations.

13.3.2.1 *Assuming proportional hazards, based on the following conditions:*

- Survival times are exponentially distributed with (at least approximately) constant hazards in both treatment arms
- The control arm will have a median survival time (MST) of 22 months (monthly hazard of 0.03151) from study entry
- The experimental arm will have a MST of 28 months (monthly hazard of 0.02476) from study entry

856 eligible patients will provide at least 90% power to detect an increase in MST from 22 months to 28 months with a 1-sided α = 0.05.

13.3.2.2 *Assuming non-proportional hazards, based on the following conditions*:

- Survival times are segment-wise exponentially distributed with non-constant overall hazards in both treatment arms, with a smaller hazard ratio within the first year and increasing into years 2 and 3 (1-yr HR=0.90; 2-yr HR=0.63; 3-yr HR=0.65).
- The control arm will have a 3-year survival of 29%
- The experimental arm will have a 3-year survival of 39%

856 eligible patients will provide at least 90% power to detect an increase in 3-year survival from 29% to 39% with a 1-sided α = 0.05.

13.3.3 Power Calculations for QoL: Health Related Quality of Life (HRQOL) FACIT-Fatigue (FACIT-F) and PROMIS-Fatigue

The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F) and National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue will be used to measure HRQOL. The primary HRQOL endpoint will be to determine if baseline FACIT-F scores are correlated with overall survival. The FACIT-F and PROMIS Fatigue tools are described in Sections 1.7.2 and 1.7.3 respectively, as well as Section 11.3. Based on work done by Robinson (details in Section 1.7.2), FACIT-F scores predicted survival when a baseline FACIT–F score of 30 was used as the cut-point for defining high (≤30) and low (> 30) fatigue. Four hundred evaluable patients will provide at least 90% power to detect a HR of 0.70 between low and high fatigue using a baseline FACIT-F cut-point of 30, with a 1-sided alpha of 0.05. The FACIT-F and PROMIS will be collected on all cases participating in this portion of the trial and will be collected at five time points: pretreatment (baseline), at the time of evaluation for progression following the first-step randomization treatment, 9, 12, and 24 months from start of first-step registration treatment. Secondary endpoints include change in FACIT-F from baseline, PROMIS fatigue scores correlating with overall survival, and change in PROMIS fatigue scores from baseline Protocol-eligible patients providing a baseline FACIT-F score will be included in the HRQOL primary endpoint analysis. To allow for patients agreeing to participate in the HRQOL portion of the trial, not completing FACIT-F at baseline and/or attrition following start of treatment, a total of 500 patients will be recruited.

13.3.4 Patient Accrual

Patient accrual is projected to be 14 cases per month, with a ramp-up period in the first 6 months. The expected monthly accrual in months 1-3 and months 4-6 following activation are 0 and 3, respectively.

This study will use a stricter rule than the CTEP early stopping guidelines for slow accruing trials:

- If the average monthly accrual rate by 2 years following activation is below 10 cases per month (< 75% of projected), the study team will discuss potential amendments with CTEP and the NCI GI Steering Committee to determine what study questions will be able to be answered in a timely fashion.

13.4 Interim Analysis

Overall and disease-free survival will be estimated by the Kaplan-Meier method.[Kaplan, 1958] The distribution of overall survival estimates between the two arms for both primary endpoint questions will be compared using the log rank test.[Mantel, 1966] Survival time for the erlotinib question will be measured from the date of first randomization (gemcitabine vs. gemcitabine/erlotinib) to the date of death or last follow-up. Survival time for the chemoradiation question will be measured from the date of second randomization (chemotherapy vs. chemotherapy followed by chemoradiation) to the date of death or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with overall survival.

13.4.1 Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pretreatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm.
- compliance rates of treatment delivery

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoints, overall survival, or any secondary endpoints, with the exception of reporting of adverse events.

13.4.2 Significance Testing for Early Termination and/or Reporting

13.4.2.1 *Erlotinib Question (First Randomization) Primary Endpoint: Overall Survival*

Three interim significance tests of treatment difference are planned. The timing of the interim analyses will be based on primary endpoint events, deaths. Under the alternative hypothesis that the addition of erlotinib will increase overall survival (either MST from 22 months to 28 months under the proportional hazards assumption or 3-year overall survival from 29% to 41% under the proportional hazards assumption), the number of events needed and the nominal significance levels for rejecting the H_0 (efficacy) or the H_1 (futility) for each of these three interim analyses are shown in the table below:

Table 1: Nominal Significance Levels for Interim Analyses

Interim Analysis	Efficacy: Reject H_0 if $p(H_0) \leq$	Futility: Reject H_1 if $P(H_1) \leq$	# Events
#1	0.001	0.005	152
#2	0.001	0.005	304
#3	0.001	0.005	455

At each planned interim analysis, the one-sided p-value from the log-rank test assessing treatment efficacy with respect to overall survival will be compared to the nominal significance levels in Table 1. The levels for testing the null hypothesis are based on the Haybittle-Peto method. If the computed p-value for efficacy is less than or equal to the nominal significance level boundary for rejecting the H_0 (efficacy), then accrual to the

gemcitabine only arm will be stopped (if applicable), it will be concluded that the overall survival rate of the erlotinib arm is higher than that of the non-erlotinib arm and the results will be reported. If accrual is not completed, patients will continue to be entered onto the erlotinib arm in order to answer the chemoradiation question (second randomization). For futility, the alternative hypothesis will be tested using rule C from Freidlin and Korn at a significance level of 0.005. [Freidlin, 2002] If the p-value is less than or equal to the nominal significance level boundary for rejecting the H_1 (futility), then accrual will be stopped to the gemcitabine+ erlotinib arm (if applicable) and it will be reported that it cannot be concluded that the overall survival rate of the erlotinib arm is higher than that of the non-erlotinib arm. If accrual is not completed, patients will continue to be entered onto the gemcitabine only arm in order to answer the chemoradiation question (second randomization). If neither of these boundaries is crossed, accrual (if applicable) and follow-up will continue until the next interim or final analysis.

Following the required number of deaths for each planned interim analysis, the blinded efficacy/futility results will be reported to the RTOG DMC, in addition to accrual, distributions of pretreatment characteristics, frequency and severity of adverse events, and compliance with protocol treatment.

13.4.2.2 Chemoradiation Question (Second Randomization) Primary Endpoint: Overall Survival

Three interim significance tests of treatment difference are planned. The timing of the interim analyses will be based on primary endpoint events, deaths. Under the alternative hypothesis that chemotherapy followed by adjuvant radiation and concurrent capecitabine will increase overall survival (MST from 17 months to 22.5 months from the second randomization) for patients with resected head of pancreas adenocarcinoma who are disease free after adjuvant chemotherapy, the number of events needed and the nominal significance levels for rejecting the H_0 (efficacy) or the H_1 (futility) for each of these three interim analyses are shown in the table below:

Table 2: Nominal Significance Levels for Interim Analyses

Interim Analysis	Efficacy: Reject H_0 if p (H_0) ≤	Futility: Reject H_1 if p (H_1) ≤	# Events
#1	0.001	0.005	113
#2	0.001	0.005	225
#3	0.001	0.005	337

At each planned interim analysis, the one-sided p-value from the log-rank test assessing treatment efficacy with respect to overall survival will be compared to the nominal significance levels in Table 1. The levels for testing the null hypothesis are based on the Haybittle-Peto method. If the computed p-value for efficacy is less than or equal to the nominal significance level boundary for rejecting the H_0 (efficacy), then accrual will be stopped (if applicable), it will be concluded that the overall survival rate of the chemoradiation arm is higher than that of the non-chemoradiation arm and the results will be reported. For futility, the alternative hypothesis will be tested using rule C from Freidlin and Korn at a significance level of 0.005. [Freidlin, 2002] If the p-value is less than or equal to the nominal significance level boundary for rejecting the H_1 (futility), then accrual will be stopped (if applicable) and it will be reported that it cannot be concluded that the overall survival rate of the chemoradiation arm is higher than that of the non-chemoradiation arm. If neither of these boundaries is crossed, accrual (if applicable) and follow-up will continue until the next interim or final analysis.

Following the required number of deaths for each planned interim analysis, the blinded efficacy/futility results will be reported to the RTOG DMC, in addition to accrual, distributions of pretreatment characteristics, frequency and severity of adverse events, and compliance with protocol treatment.

13.4.3 Analysis for Reporting the Initial Treatment Results

13.4.3.1 *Erlotinib Question (First Randomization) Primary Endpoint: Overall Survival*

The primary hypothesis of the erlotinib question is whether the addition of erlotinib will increase overall survival (either MST from 22 months to 28 months under the proportional hazards assumption or 3-year overall survival from 29% to 41% under the proportional hazards assumption) for patients with resected head of pancreas adenocarcinoma. This major analysis will occur after all patients have potentially been followed for 3 years, unless an early stopping rule is satisfied. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rate of treatment delivery
- observed results with respect to the primary and secondary endpoints applicable to the erlotinib question

All eligible patients randomized will be included in the comparison and will be grouped in the analysis by assigned treatment from the first randomization (gemcitabine vs. gemcitabine/erlotinib). The primary hypothesis of treatment benefit will be tested using the log-rank statistic with a significance level of 0.05, given that the three interim analyses were carried out per Section13.4.2.1. Additionally, analyses of treatment effect will be performed using the Cox proportional hazard model with the three stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms. Where feasible, treatment comparisons with respect to the primary endpoint (overall survival) will be compared within gender, ethnic and racial categories.

13.4.3.2 *Chemoradiation Question (Second Randomization) Primary Endpoint: Overall Survival*

The primary hypothesis of the chemoradiation question is whether chemotherapy followed by adjuvant radiation and concurrent capecitabine will increase median survival for patients with resected head of pancreas adenocarcinoma who are disease free after adjuvant chemotherapy. This major analysis will occur after all patients randomized to the chemoradiation portion of the trial have potentially been followed for 2.5 years from the second randomization unless an early stopping rule is satisfied. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rate of treatment delivery
- observed results with respect to the primary and secondary endpoints applicable to the chemoradiation question

All eligible patients randomized to the chemoradiation portion of the trial will be included in the comparison and will be grouped in the analysis by assigned treatment from the second randomization (chemotherapy vs. chemotherapy followed by chemoradiation). The primary hypothesis of treatment benefit will be tested using the log-rank statistic with a significance level of 0.05, given that the three interim analyses were carried out per Section13.4.2.2. Additionally, analyses of treatment effect will be performed using the Cox proportional hazard model with the four stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms). Where feasible, treatment comparisons with respect to the primary endpoint (overall survival) will be compared within ethnic and racial categories.

13.4.4 Analysis of HRQoL Endpoints

13.4.4.1 *FACIT-F Scoring and Analysis*

13.4.4.1.1 The FACIT-F will be scored per the FACIT-F Scoring Guidelines (Version 4 www.facit.org), with higher scores indicating less fatigue.

13.4.4.1.2 The primary objective in the HRQoL analysis is determine if baseline FACIT-F scores are correlated with overall survival; specifically if patients with baseline FACIT-F scores > 30

(low fatigue) have better overall survival than patients with baseline FACIT-F scores ≤ 30 (high fatigue).

13.4.4.1.3 The primary HRQoL hypothesis will be tested using the log-rank statistic with a significance level of 0.05. Additionally, analyses of fatigue effect will be performed using the Cox proportional hazard model with first step-randomization treatment, nodal status (involved vs. uninvolved), serum CA19-9 (≤ 90 vs. > 90-180), and surgical margins (positive vs. negative) included as fixed covariates, as well as any factors that show an imbalance between patients with low and high FACIT-F scores.

13.4.4.2 Analysis for Secondary Endpoints Related to HRQoL

13.4.4.2.1 *Missing Data*

The distributions of HRQoL data collection patterns over all collection points. To inspect the missing data mechanism for each tool, we will use at least a graphical method. A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples.

If the cause of missing data is MCAR, listwise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data.

If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline QOL score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method such as multiple imputation will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism [Donaldson, 2005] and then an imputation method such as multiple imputation will be applied. All results from the imputed analysis using the multiple imputation will be compared to the complete case analysis results to assess any potential biases.

13.4.4.2.2 The PROMIS Fatigue will be scored per the PROMIS Fatigue Scoring Guidelines (Version 1 www.nihpromis.org).

13.4.4.2.3 *Exploratory Analyses*

The baseline PROMIS Fatigue scores will be analyzed to determine if there is a cut-point (adjusting for multiple comparisons) that correlates with overall survival using the log-rank statistic. If a cutpoint is determined, addition analyses of fatigue effect will be performed using the Cox proportional hazard model with first step-randomization treatment, nodal status (involved vs. uninvolved), serum CA19-9 (≤ 90 vs. > 90-180), and surgical margins (positive vs. negative) included as fixed covariates, as well as any factors that show an imbalance between patients with low and high PROMIS Fatigue scores.

13.4.5 Data and Safety Monitoring

This study will be reviewed by the RTOG Data Monitoring Committee (DMC) on a semi-annual basis in January and June for accrual (while applicable) and adverse events; as well as for efficacy/futility as specified in Sections 13.4.2.1 and 13.4.2.2.

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.

13.5 Statistical Methods Analysis for Laboratory Correlative Section

It is anticipated that approximately 856 eligible patients will be registered to this trial. Specimen submission is a requirement; taking into account a 90% submission rate (accounting for some inability to obtain specimens and for some specimens to be inadequate to obtain marker data), we will have approximately 770 specimens available for these correlative studies.

13.5.1 There are two primary aims for this study:

- To assess whether patients with EMT phenotype fail to benefit from the addition of erlotinib, while those without this phenotype experience improved clinical outcome when erlotinib is combined with gemcitabine therapy.

- To determine the influence of K-Ras mutations on benefit from erlotinib

13.5.2 Analysis Plan

The primary clinical endpoint of this study is overall survival, defined from the date of study registration to the date of death or to the date the patient was last known to be alive (censored observation). Analyses will be done using the Cox proportional hazards model.[Cox, 1972] This technique will allow us to assess marker effects while adjusting for treatment assignment, and the effect of other known prognostic factors such as nodal status, margin status, and tumor diameter. The primary aims of the trial translate statistically into a test of marker by treatment interaction, which can be assessed using this model.

Traditional descriptive statistics and summary tables will be generated for all data from this study. The frequencies of various markers are not well known in adjuvant pancreatic cancer. With 770 patients we will be able to estimate the frequency of individual markers to within ± 3.6%.

13.5.3 Power Assessments

The primary aims of interest are to assess the relationship between EMT phenotype and treatment with respect to overall survival, and between EGFR loop activation and treatment with respect to overall survival.

Power estimates are influenced in part by the frequency of the marker of interest in this population. Because these frequencies are not well known in this population, we provide estimates based on either a relatively equal split, and under the more extreme assumption of 10% EMT phenotype and 90% EGFR.

Because there are two primary objectives, power calculations have been based on one-sided .025 tests of the interactions to preserve an overall type-I error rate of 5%. For purposes of assessing EMT, the hypothesis is that there will be no benefit to treatment in the presence of the EMT phenotype. This translates into a hazard ratio of 1 between the chemotherapy treatment arms in this subset. Among patients without the EMT phenotype, it is assumed that there will be improvement in the erlotinib arm. In this situation, the hazard ratio for the interaction can be interpreted as the hazard ratio between the 'standard' arm and the erlotinib arm.

Similarly, for the EGFR loop activation, it is assumed that those without activated EGFR will fail to benefit from the addition of erlotinib, while those with activated EGFR will show benefit. In this case, the hazard ratio for the interaction would be the same as the hazard ratio for the treated arms in the subset with EGFR activation.

Table 1 provides power estimates for selected levels of interaction for either the EMT or EGFR endpoint, under three ranges of splits for the frequency of presence/absence of the marker. Because the treatment trial is powered for an overall hazard ratio (under the proportional hazards assumption) of at least 1.3 (control/experiment), this implies that we would expect a much higher interaction hazard ratio, since the treatment effect is hypothesized to occur only in subsets of the population. It should also be noted that these calculations assume independence between these markers, when in fact there may be some correlation between them.

Table 1: Power to detect selected levels of an interaction between EMT phenotype, EGFR loop activation, or kRAS status and treatment assignment with respect to overall survival, assuming a .025 one-sided test and 770 assessable specimens.

Interaction HR	Power 50:50 split	Power 25:75 (75:25) split	Power 10:90 split
1.6	.90	.80 (.79)	.49
1.7	.95	.89 (.88)	.59
1.8	.98	.94 (.93)	.68
1.9	.99	.97 (.97)	.76

Note that these splits can be read as follows; as an example, the 25:75 split gives the resulting power for either 25% EMT present, or 25% inactive EGFR. Similarly, in parenthesis, the 75:25

split gives the power for kRAS, under the assumption that 25% of the patients are kRAS WT, and is the subset which predicts response to erlotinib.

Thus, if the distribution of the markers is not too extreme, we have 80% or higher chance of observing interactions on the order of 1.6 or higher.

13.5.4 Secondary Objectives

We will also assess whether overexpression of c-Met and RON are correlated with treatment outcome, using IHC for RON, C-met and matriptase-1, and QPRC to quantify HGF and HGFL. These markers will initially be analyzed as either positive/negative or by categorizing into high/low for measures of expression. This is due to the fact that the distributions of these continuous measures often do not lend themselves to a linear term in the Cox model. An initial categorization at the median is one approach; alternatives to be explored will be to select the split that maximizes the logrank statistic comparison of survival between the two levels. It should be emphasized that there is no single 'best' way to dichotomize gene expression for a single marker, and thus we will need to be cautious in the way we generalize these data.

Another aim will be to compare the frequency of markers between baseline pre-treatment samples and characteristics of the tumor at recurrence.

We will also assess the relationship of the markers noted above to disease-free survival.

13.6 Gender and Minorities

Both men and women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between race/ethnicity and treatment. Based on RTOG 9704, it is projected that 57% of the patients will be men and 43% women; 2% will be of Hispanic or Latino ethnicity; racial distribution will be 90% white, 7% black or African American, and 1% each of American Indian or Alaskan Native, Asian, and Native Hawaiian or other Pacific Islander. The following table lists the projected accrual by ethnic and racial categories. Assuming no differences between the ethnicities, or among the races, the statistical power for detecting the hypothesized treatment difference is 0.78 for males and 0.68 for females for the erlotinib question and 0.68 for males and 0.57 for females for the chemoradiation question. The statistical power for non-whites, and Hispanic/Latino is too low for any meaningful treatment comparisons.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	9	11	20
Not Hispanic or Latino	399	531	930
Ethnic Category: Total of all subjects	408	542	950
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	5	5	10
Asian	5	5	10
Black or African American	37	28	65
Native Hawaiian or other Pacific Islander	5	5	10
White	356	499	855
Racial Category: Total of all subjects	408	542	950

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APPENDIX I

Informed Consent Template for Cancer Treatment Trials
(English Language)

RTOG 0848
A Phase III Trial Evaluating Both Erlotinib and Chemoradiation as Adjuvant Treatment for Patients with Resected Head of Pancreas Adenocarcinoma

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 pancreatic cancer that was removed by surgery. You are eligible for this study because there was no visible cancer left behind and not more than 8 weeks have passed since your operation.

Why is this study being done?

The standard treatment for patients with pancreatic cancer that was removed by surgery is to receive the chemotherapy drug gemcitabine. In this study, you will get either gemcitabine alone or gemcitabine combined with erlotinib. Erlotinib is a pill that may help treat cancers by blocking a gene that is important in cancer growth. The use of erlotinib to try to prevent the recurrence of pancreatic cancer after surgery is investigational. This study will compare the effects, good and/or bad, of the drug erlotinib in combination with gemcitabine to gemcitabine alone for patients with pancreatic cancer that was removed by surgery to find out which is better.

Following completion of 5 months of gemcitabine (with or without erlotinib), all patients will be evaluated by CT scan to see if the tumor has not grown back (progressed). We expect that most patients will not have signs of progression although a few patients may show signs of progression at this point. Patients showing progression will no longer receive treatment on this study. For patients who remain without evidence of progression, half will then get one additional month of gemcitabine (with or without erlotinib). The other half will get one additional month of gemcitabine (with or without erlotinib) and then will get radiation treatments with a fluoropyrimidine for about 5 ½ weeks. (A fluoropyrimidine is a type of chemotherapy drug that may help radiation be more effective). Therefore, this study will also determine the effects, good and/or bad, of radiation for patients who remain disease-free after gemcitabine chemotherapy.

How many people will take part in the study?

About 950 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study

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

- Physical Exam
- Blood Tests
- Abdominal/Pelvic CT/MRI Scan
- Chest X-Ray or Chest CT
- Pregnancy Test

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. They are part of regular cancer care.

• Physical Exam	Monthly during gemcitabine and weekly during radiation treatment
• Blood tests	Weekly while you are on the study
• Abdominal CT/MRI	After 5 months of gemcitabine with or without erlotinib
• Chest X-ray or CT	After 5 months of gemcitabine with or without erlotinib

When you enter the study, it is required that the study doctor send the block of tumor tissue obtained at the time of your surgery and some blood (2 tablespoons) to the central tissue bank. Scientists will study your tumor tissue and blood to try to learn more about pancreatic cancer and determine what characteristics of pancreatic cancer cells predict cancer growth.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in any group. Treatments are given in an outpatient setting.

If you are in group 1 (Arm 1): Gemcitabine weekly by vein over 30 minutes for 3 weeks, then 1 week off, for 5 months. (1 cycle = 1 month)

If you are in group 2 (Arm 2): Gemcitabine weekly by vein over 30 minutes for 3 weeks, then 1 week off, for 5 months and erlotinib, 1 pill per day on an empty stomach for 5 months

(3/4/10) When you have completed 5 months of treatment, you will have a CT scan and chest x-ray. If your cancer has grown back, you will be removed from study treatment, you will not be randomized again to one of two treatments. Your doctors will discuss with you what options are best for you, and you will be seen in follow-up visits as described below.

If, after 5 months of chemotherapy your cancer has not grown back you will be randomized again to one of two treatments. The chances of receiving either treatment are about equal. You will be treated with one of the following:

If you are in group 3 (Arm 3): One additional cycle of the same chemotherapy you received in the first 5 months of this study (either gemcitabine alone or gemcitabine with erlotinib).

If you are in group 4 (Arm 4): One additional cycle of the same chemotherapy you received in the first 5 months of this study (either gemcitabine alone or gemcitabine with erlotinib). In addition, you will receive radiation and fluoropyrimidine. Radiation will be given to the area where your tumor was once a day, Monday through Friday for 5 ½ weeks *(28 radiation treatments)*. Fluoropyrimidine will be given with the radiation. Fluoropyrimidine is a chemotherapy drug that helps radiation work better. There are two forms of fluoropyrimidine. You may receive a pill form of fluoropyrimidine called capecitabine, which is taken twice a day, Monday through Friday on radiation days for 28 days. Alternatively, you may receive the form called 5-FU, which is given by vein continuously, 7 days per week, for 5 ½ weeks throughout radiation. If you receive the intravenous 5-FU you will need a special IV tube placed into a large vein in your arm, neck or chest and a small pump to give the drug. This pump weighs about seven ounces and would be worn by you throughout the 5 ½ weeks. You and your doctor will decide which form of fluoropyrimidine (capecitabine or 5-FU) is best for you.

When treatment is finished you will need the following

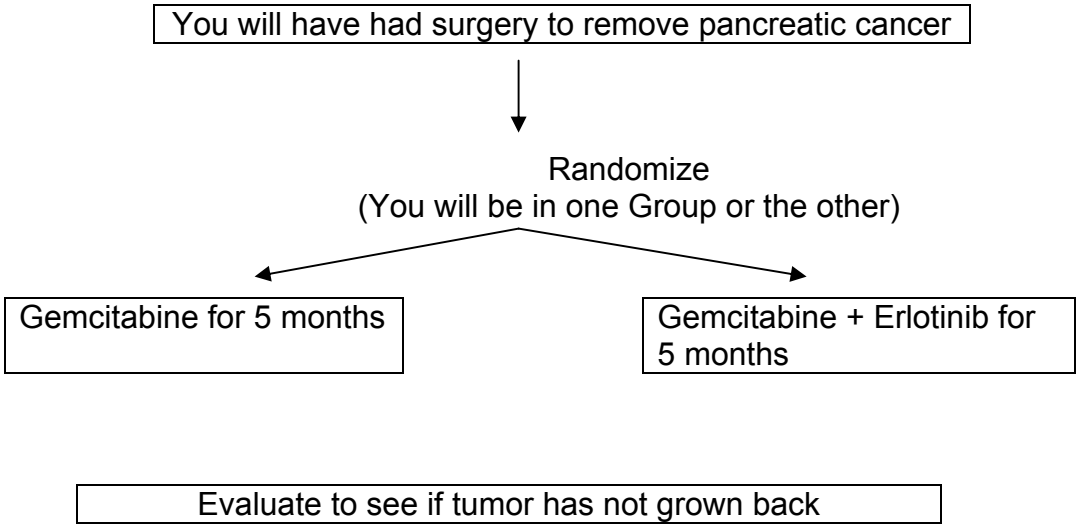
For patients who do not receive Arm 3 or 4 treatment:

- Physical Exam — Every 6 months for 2 years then annually

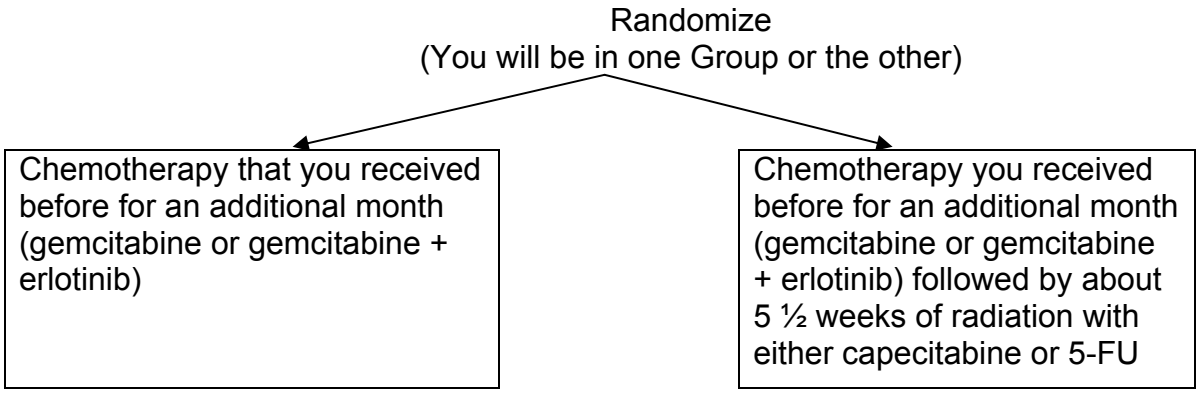
For patients who receive Arm 3 or 4 treatment:

- Physical Exam — Every 3 months for 2 years, every 6mo x 3yrs then annually
- Abdominal CT/MRI — Every 3 months for 2 years, every 6mo x 3yrs then annually
- Chest X-ray or CT — Every 3 months for 2 years, every 6mo x 3yrs then annually

(3/4/10) 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.



If there is no evidence of progression:



If there is evidence of progression: You will no longer receive treatment on this study, but you will be seen in follow-up visits

How long will I be in the study?

You will be asked to take 5 months of gemcitabine (with or without erlotinib). Radiation and fluoropyrimidine takes 5 ½ weeks if you are in an arm receiving the radiation and 5-FU treatment. If you are in group 1 (Arm 1) or 2 (Arm 2), you will have follow-up exams every six months for two years and then every year for your lifetime to record whether your cancer grows back.

If you are in group 3 (Arm 3) or 4 (Arm 4), you will have follow-up exams every three months for two years, every six months for three years, and then every year for your lifetime to record whether your cancer grows back.

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 drugs or radiation can be evaluated. 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?

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 taking the drugs and/or radiation. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the Gemcitabine include those which 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
- Vomiting
- Constipation

- Change in liver function that could cause jaundice (yellowing of skin)
- Excess protein in the urine
- Abnormal kidney function tests

Rare but serious

- A severe skin reaction called Stevens-Johnson Syndrome, a painful red or purplish rash that spreads and blisters, eventually causing the top layer of your skin to die and shed
- Inflammation or scarring of the lung with shortness of breath and cough
- Kidney and liver failure
- Cardiac dysfunction such as heart attack, congestive heart failure (heart unable to pump enough blood throughout the body), and atrial fibrillation (problem with the speed or rhythm of the heartbeat.

Risks and side effects related to the Erlotinib include those which are (6/8/10):

Likely

- Diarrhea
- Vomiting
- Fatigue or tiredness
- Loss of appetite
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)

Less Likely

- Inflammation (swelling and redness) of the conjunctiva (the outermost layer of the eye and the inner surface of the eyelids). Commonly called "pink eye".
- Dry eye
- Eyelash in-growth and/or thickening
- Belly pain
- Dry mouth
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Irritation or sores in the lining of the mouth
- Nausea or the urge to vomit
- Infection of the skin
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Dehydration (when your body does not have as much water and fluid as it should)
- Taste changes
- Headache or head pain
- Cough
- Shortness of breath
- Nose bleed
- Inflammation (swelling and redness) of the lungs
- Hair loss
- Dry skin

- Loss of some or all of the finger or toenails
- Itching
- Acne

Rare but serious

- Hole in the outer layer of the eye
- Inflammation (swelling and redness) of the cornea (the transparent front cover of the eye)
- Hole in a part(s) of the digestive tract
- Liver failure
- Bleeding in the brain
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- Swelling and redness of the skin on the palms of the hands and soles of the feet
-

Dangerous interaction between erlotinib and warfarin (Coumadin®): If you are taking warfarin or Coumadin® (medicine to prevent blood clotting), erlotinib may change the way your blood clots. If you need to take warfarin, your doctor will regularly check for changes in blood clotting time.

Patients who will be taking erlotinib, should wear sun screen protection, hat, and long sleeve shirt as the sun can make the skin rash worse.

Risks Associated with Fluoropyrimidine:
You and your doctor will decide whether it is best for you to receive the pill form of fluoropyrimidine (capecitabine) or the IV form (5-FU). The leaders of this study believe the effectiveness of the IV and pill forms are the same. The general side effects of the pill (capecitabine) and IV (5-FU) forms of fluoropyrimidine are similar. However, in some patients, capecitabine may cause more diarrhea and nausea. These potential gastrointestinal side effects of capecitabine are balanced by the inconvenience of a continuous 5-FU infusion and the need for the minor surgical placement of a special type of intravenous (PICC line or port-a-cath) and the need to carry a small pump for 5 ½ weeks.

Risks and side effects related to the fluoropyrimidine include those which 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
- Change in liver function that could cause jaundice (yellowing of skin)
- Unsteadiness

Rare but serious

- Chest pain or irregular heartbeat

Dangerous interaction between capecitabine and warfarin (Coumadin®): If you are taking warfarin or Coumadin® (medicine 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 doctor will regularly check for changes in blood clotting time. The IV drug 5-FU does not interact as significantly with warfarin.

Risks and side effects related to the radiation include those which 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: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs 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. It has been proven that gemcitabine will reduce the chance that this cancer will come back and that this will increase your lifespan. It is not proven whether the addition of erlotinib to gemcitabine or the addition of radiation and fluoropyrimidine following gemcitabine will reduce the risk of pancreatic cancer recurring for patients with pancreatic cancer that has already been removed. Based on other studies there are reasons to believe that these treatments may be helpful and this trial is being done to try to find out whether they really are. We do know that the information from this study will help researchers learn more about the treatment of 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

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 Southwest Oncology Group

- The European Organization for the Research and Treatment of Cancer
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
- OSI Pharmaceuticals, the company that makes erlotinib

What are the costs of taking part in this study?

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

The NCI will supply the study agent, erlotinib, at no charge while you take part in this study. The NCI does not cover the cost of getting the erlotinib 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 erlotinib to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get the erlotinib from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.

- If there is no erlotinib available at all, no one will be able to get more, and the study would close.

If a problem with getting erlotinib occurs, your study doctor will talk to you about these options.

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

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

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

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

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the 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 Monitoring Committee (DMC) will be regularly meeting to monitor safety and other data related to this study. The Committee 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 [for each study].

Consent Form for Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This "Quality of life" study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete 2 questionnaires: before treatment, and then at 5-6, 9, 12 and 24 months after your treatment has started. It takes about 5 minutes or less to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the 2 questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the two Quality of Life Questionnaires.

YES NO

Consent Form for Use of Tissue, Blood, and Urine for Research

About Using Tissue, Blood, and Urine for Research (5/23/11)

Your cancer has been removed by surgery. To participate in the main part of this study, you must agree to have your tumor tissue and blood sample sent to the tissue bank to be used for studies that are essential components of this clinical trial. Therefore, permission to use the tissue block and blood sample is mandatory for your participation in the main study.

We would like to keep some of the tissue that is left over for future research. The use of your tissue, blood and urine for future research is optional. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available at http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm

If your cancer comes back and an additional biopsy is needed, your doctors ask permission to send additional tumor tissue and blood to a research lab but this is not required.

In addition, we would like to keep some of your urine for future research. We would collect about 5 tablespoons of your urine before you start treatment. If you agree, the urine will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your tissue, blood, urine 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, blood, urine will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and blood and urine 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, blood, urine 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, blood, and urine. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it and leftover blood and urine will be destroyed. However, tissue, blood, and urine already used and data obtained from it will remain part of the study data.

In the future, people who do research may need to know more about your health. While your doctor/institution may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue, blood, and urine are used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

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

Benefits

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

Risks

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

Making Your Choice

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

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

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*
   - *Urine ☐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*
   - *Urine ☐Yes ☐ No*

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

4. *If my cancer comes back, specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:*
   - *Tissue ☐Yes ☐ No*
   - *Blood ☐Yes ☐ No*

5. If my cancer comes back, 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*

Where can I get more information? (4/12/12)

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.**

Participant _____

Date _____

APPENDIX II (5/23/2011)
STUDY PARAMETER TABLE

Assessments	**Pre-Treatment**			**During Treatment** (see Section 11 for further details)				**Follow up**	
	31 days prior to regis-tration	21 days prior to registration	14 days prior to regis tration	Days 1,8,15 of each cycle gemcitabine +/- erlotinib	Monthly during gemcitabine +/- erlotinib	Within 3 weeks after completing the 5th cycle of chemo	Wkly during chemo /RT	**For pts on Arms 1 or 2 ONLY** every 6mo x 2yrs then annually	**For pts on Arms 3 or 4** every 3mos x 2yrs, every 6mo x3 yrs then annually
History	X								
Physical with weight and vital signs	X				X	X	X	X	X
Performance status			X		X	X		X	X
CT/MRI of abdomen/pelvis	X					X			X
Chest CT or x-ray	X					X			X
CBC w/ diff; platelets & ANC		X		X	X	X	X		
SGOT; total bilirubin creatinine		X			X	X			
Na, K, Cl, CO_2, glucose, BUN		X			X	X			
Post-op CA19-9		X						X	X
Serum pregnancy test (if applicable)			X						
Quality of Life Evaluation[a]	See Table Below for QOL assessments								
Tissue, blood, and urine submission	Tissue from resection and blood is mandatory and must be submitted prior to start of treatment								
Adverse event eval (and as needed based on reporting requirement)				X	X	X	X	X	X

[a] **Recommended but not mandatory**

APPENDIX II Continued

QOL

PRIOR TO ANY PROTOCOL TREATMENT	after completion of Arm I or 2 systemic therapy but prior to CLINICAL EVALUATION FOR PROGRESSION	9 MO FROM THE START OF ARM 1 OR 2 THERAPY	12 MO FROM THE START OF ARM 1 OR 2 THERAPY	24 MO FROM THE START OF ARM 1 OR 2 THERAPY
X	X	X	X	X

APPENDIX III
ZUBROD PERFORMANCE SCALE

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

APPENDIX IV

STAGING FOR PANCREAS
AJCC, 6th Edition

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

*This also includes the “PanInIII” classification

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

APPENDIX V

Example of Surgical Pathology Reporting Form
(www.cap.org/apps accessed January 8, 2009)

Pancreas (Exocrine)

Protocol applies to all carcinomas of the exocrine pancreas.

Protocol revision date: January 2005
Based on AJCC/UICC TNM, 6th edition

Procedures

- **Cytology** (No Accompanying Checklist)
- **Incisional Biopsy** (No Accompanying Checklist)
- **Partial Pancreatectomy**
- **Pancreaticoduodenectomy (Whipple Resection)**

Author
Carolyn C. Compton, MD, PhD
Department of Pathology, McGill University, Montreal, Quebec, Canada
For the Members of the Cancer Committee, College of American Pathologists
Previous contributors: Donald E. Henson, MD; Carlos Fernandez-del Castillo, MD; Andrew L. Warshaw, MD; Christopher Willett, MD

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The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with the document. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

Pancreas (Exocrine) • Digestive System CAP Approved
* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2005
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

PANCREAS (EXOCRINE): Resection

Patient name:
Surgical pathology number:
Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Pancreaticoduodenectomy (Whipple resection), partial pancreatectomy
___ Pancreaticoduodenectomy (Whipple resection), total pancreatectomy
___ Pylorus sparing pancreaticoduodenectomy, partial pancreatectomy
___ Pylorus sparing pancreaticoduodenectomy, total pancreatectomy
___ Partial pancreatectomy, pancreatic body
___ Partial pancreatectomy, pancreatic tail
___ Other (specify): _____
___ Not specified

Tumor Site (check all that apply)
___ Pancreatic head
___ Uncinate process
___ Pancreatic body
___ Pancreatic tail
___ Not specified

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

***Other Organs Resected**
*___ None
*___ Spleen
*___ Gallbladder
*___ Other(s) (specify): _____

MICROSCOPIC

Histologic Type
___ Ductal adenocarcinoma
___ Mucinous noncystic carcinoma
___ Signet-ring cell carcinoma
___ Adenosquamous carcinoma
___ Undifferentiated (anaplastic) carcinoma
___ Undifferentiated carcinoma with osteoclast-like giant cells
___ Mixed ductal-endocrine carcinoma
___ Serous cystadenocarcinoma

___ Mucinous cystadenocarcinoma – invasive
___ Invasive papillary-mucinous carcinoma
___ Acinar cell carcinoma
___ Acinar cell cystadenocarcinoma
___ Mixed acinar-endocrine carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (ductal carcinoma only)

___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): _____

Pathologic Staging (pTNM)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
___ pT1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
___ pT2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
___ pT3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
___ pT4: Tumor involves the celiac axis or the superior mesenteric artery

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
*___ N1a: Metastasis in single regional lymph node
*___ N1b: Metastasis in multiple regional lymph nodes
Specify: Number examined ___
Number involved: ___

Distant Metastasis (pM)
___ pMX: Cannot be assessed
___ pM1: Distant metastasis
*Specify site(s), if known: _____

Margins (check all that apply)

___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm
*Specify margin (if possible): _____
___ Carcinoma in situ absent at ductal margins
___ Carcinoma in situ present at common bile duct margin
___ Carcinoma in situ present at pancreatic parenchymal margin
___ Margin(s) involved by invasive carcinoma
___ Posterior retroperitoneal (radial) margin: posterior surface of pancreas
___ Uncinate process margin (non-peritonealized surface of the uncinate process)
___ Distal pancreatic margin
___ Common bile duct margin
___ Proximal pancreatic margin
___ Other (specify): _____

***Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)**
*___ Absent
*___ Present
*___ Indeterminate
***Perineural Invasion**
*___ Absent
*___ Present
***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Pancreatic intraepithelial neoplasia (highest grade: PanIN ___)
*___ Chronic pancreatitis
*___ Acute pancreatitis
*___ Other (specify): _____
***Comment(s)**

Appendices VI- VIII for RTOG Biospecimen Collection (4/12/12)

RTOG FFPE Specimen Plug Kit Collection
RTOG Blood Collection Kit Instructions
RTOG Urine Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94115

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

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (STF) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the RTOG study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o 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 the slides shaking it is likely that they will break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - o 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.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) 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 e-mail: RTOG@ucsf.edu or phone: 415-476-RTOG(7864) or Fax: 415-476-5271.**

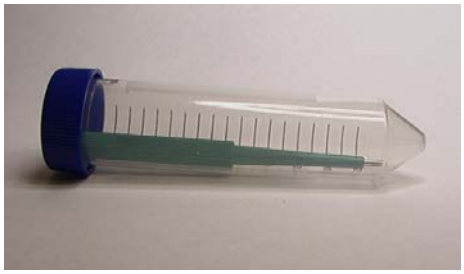
APPENDIX VI (4/12/12)
RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label punch tool with proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or email us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

*NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship: Specimen plug kit, specimen in punch tool, and all paperwork to the address below:

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 Street, Room S341
San Francisco, CA 94115

Courier Address (FedEx, UPS, etc.): For Trackable FFPE shipments
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

APPENDIX VII (4/12/12)
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or blood (as specified by protocol):

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) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers

Specimen Transmittal Form and Kit Instructions

Preparation and Processing Plasma and Whole Blood:

(A) Plasma: 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, time, and time point, 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 minutesat 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 greater 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 to -90°C
6. Store frozen plasma -70 to -90° C until ready to ship on dry ice
7. See below for storage conditions.

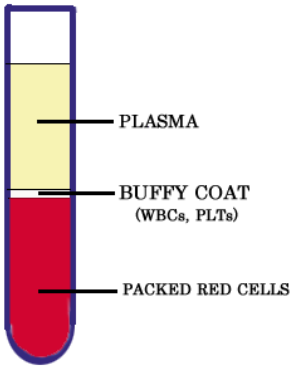
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection timepoint on STF.

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

- ❑ Label as many 1 ml 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 labeled "blood" 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 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.



PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and includes collection time point on STF

Storage and Shipping

Freezing and Storage:

- ☐ Freeze Blood samples in a -80C 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- Canada Mon-Tues).

  - OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).

  - OR:
  - Samples can be stored in liq. nitrogen vapor phase (ship out Monday-Wednesday only- Canada Mon-Tues).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** 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 from 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 :

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

APPENDIX VIII (4/12/12)
RTOG URINE COLLECTION KIT/INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

This Kit contains:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process

A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:

- Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
- After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
- After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
- Finish voiding the bladder into the toilet bowl

- Aliquot 5-10 mls of urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimens as “urine”.
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with RTOG study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -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; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified
- Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- Place sealed 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 from 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.* ***Add padding to avoid the dry ice from breaking the tubes.***

- For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail 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 Street, Room S341
San Francisco, CA 94115
Contact Phone: (415) 476-RTOG(7864)

APPENDIX IX
RTOG 0848
PATIENT'S PILL DIARY- ERLOTINIB

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month of treatment
2. Record the date, the number of pills taken, and the total dose
3. Please bring the forms to your Research Nurse/Physician weekly during treatment.

Date		# of pills taken	Total Dose	Date		# of pills taken	Total Dose
1.				17.			
2.				18.			
3.				19.			
4.				20.			
5.				21.			
6.				22.			
7.				23.			
8.				24.			
9.				25.			
10.				26.			
11.				27.			
12.				28.			
13.				29.			
14.				30.			
15.				31.			
16.							

Patient's Signature:_____ Date:___-____-____

APPENDIX X
RTOG 0848
PATIENT'S PILL DIARY- CAPECITABINE

INSTRUCTIONS TO THE PATIENT:
1.Complete one form for each month of treatment
2.Record the date and number of pills each time you take them in the morning and in the evening.
3.Please return the forms to your Research Nurse/Physician weekly during treatment.

Date		AM: # of pills taken	PM: # of pills taken	Date		AM: # of pills taken	PM: # of pills taken
1.				17.			
2.				18.			
3.				19.			
4.				20.			
5.				21.			
6.				22.			
7.				23.			
8.				24.			
9.				25.			
10.				26.			
11.				27.			
12.				28.			
13.				29.			
14.				30.			
15.				31.			
16.							

Patient's Signature:_____ Date:_____

APPENDIX XI

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]	RTOG Headquarters 1818 Market Street, Suite 1600 Philadelphia, PA 19103 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility or treatment-related questions the Data Management Department at RTOG Headquarters @ 215 574 3150		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org **The CTSU Registered Member Web site is located at https://members.ctsu.org**		

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at http://members.ctsu.org

All forms and documents associated with this study can be downloaded from the RTOG 0848 Web page on the CTSU registered member Web site (https://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for RTOG 0848 registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- Sites must be credentialed for either 3D-CRT or IMRT approaches
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory From must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Pre-study requirements for patient enrollment on RTOG 0848

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.
  NOTE: Failure to perform one or more of the tests outlined in Appendix II may result in assessment of a protocol violation.

CTSU Procedures for Patient Enrollment

NOTE: There is a two-step registration process and both steps must be completed for all patients.

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon-Fri. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- Eligibility Checklist Step 1

CT/MRI must be performed after the 5th cycle of chemotherapy to evaluate patients for progressive disease. Step 2 registration must be completed for all patients at this time. However, only patients with non-progressive disease will be randomized to further treatment.

3. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- Eligibility Checklist Step 2

4. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. Please note that registration is limited to the lead group's operating hours of 8:30 AM to 5 PM ET. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.

5. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG **within the confines of RTOG's registration hours**, to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

NOTES:

Patients must be offered the opportunity to participate in the quality of life (QOL) assessment. Provided that patient consent is obtained, sites are required to administer the baseline QOL and functional assessments prior to the start of protocol treatment.

Chemotherapy must begin within 7 days following Step 1 registration.

Initiation of the first cycle of treatment for Step 2 must occur within 4 weeks of last chemotherapy dose in Step 1.

DATA SUBMISSION AND reconciliation

1. All case report forms (CRFs) associated with this study must be downloaded from the RTOG 0848 Web page located on the CTSU registered member Web site (https://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the RTOG 0848 unless an alternate location is specified in the protocol. Do not send study data to the CTSU.

3. The RTOG data center will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the RTOG data center and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP IAM account contact information current.** This will ensure timely communication between the clinical site and the RTOG data center.

special materials or substudies

1. Specimen collection for correlatives (Protocol section 10.0)

- Collect, prepare, and submit specimens as outlined in the protocol
- Kits may be requested by contacting the Biospecimen Resource (see 10.2.2.4)
- Do not send specimens, supporting clinical reports, or transmittals to the CTSU

NOTE: Tumor tissue block and peripheral blood submission at study entry are mandatory. Urine submission at study entry is highly recommended.

2. Quality of Life Substudies (Protocol section 11.0)

- FACIT-Fatigue has been translated into 49 languages and is available free of charge to institutions (see 11.3)
- PROMIS-Fatigue is available in English and Spanish only (see 11.3)

NOTE: Patients must be offered the opportunity to participate in all correlative science and QOL components of this study.

SERIOUS Adverse Event (AE) Reporting (SECTION 7.1)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (https://members.ctsu.org) or by drilling down to the Adverse Event Reporting Forms link under the documents folder of the RTOG 0848 Web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

Drug Procurement (SECTION 7.0)

Commercial agents: Gemcitabine; Capecitabine

Commercial agents: Erlotinib

Erlotinib, will be provided free of charge and distributed by NCI PMB.

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in section 7.0 of the protocol.

2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center tree on the RTOG 0848 Web page.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data System–Web (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-Web). The sponsoring Group fulfills this reporting obligation by transmitting the CDS data collected from the study-specific case report forms, via the Web to the NCI Center for Biometrics (NCICB). Cumulative CDS data are submitted quarterly.

APPENDIX XII
EORTC GROUP-SPECIFIC INFORMATION

To come