NRG ONCOLOGY
RTOG 0848

A PHASE II-R and A PHASE III TRIAL EVALUATING BOTH *ERLOTINIB (PH II-R) AND CHEMORADIATION (PH III) AS ADJUVANT TREATMENT FOR PATIENTS WITH RESECTED HEAD OF PANCREAS ADENOCARCINOMA

This trial is part of the national NCI Clinical Trials Network (NCTN) program which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN researchers: the Alliance, ECOG-ACRIN, and SWOG

***(PH II-R ERLOTINIB RANDOMIZATION COMPLETED, ARM 2 CLOSED TO ACCRUAL EFFECTIVE** (04/02/14)

Study Team (11-APR-2023)

NRG Oncology

Principal Investigator
Radiation Oncology
Ross A. Abrams, MD
See Appendix VIII

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
Mount Sinai Hospital
One Gustave L. Levy Place
Box 1128
New York, NY 10029
212-659-8609
karyn.goodman@mountsinai.org

SWOG

Medical Oncology
Lab Correlatives
Philip A Philip, MD, PhD, FRCP
Henry Ford Hospital
Division of Hematology and Oncology
2850 West Grand Boulevard
Detroit, MI 48202
313-576-8728
pphilip1@hfhs.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
Katherine A. Guthrie, Ph.D.
SWOG Statistical Center
Fred Hutchinson Cancer Research Center
PO Box 19024
1100 Fairview Ave N #M3-C102
Seattle Wa 98109
206-667-5595/FAX 206-667-4408
Kguthrie@fhcrc.org

Study Chairs continued on next page

NRG Oncology Study Chairs (Continued)

Medical Oncology
Howard Safran, MD
Rhode Island Hospital
Hematology and Oncology Division
593 Eddy Street
Providenc, RI 02903
401-444-4830
hsafran@lifespan.org

Surgical Oncology
Adam Berger, MD
Rutgers Cancer Institute of New Jersey
195 Little Albany Street
Room 3005
New Brunswick, NJ 08903
732-235-7563
ab2047@cinj.rutgers.edu

Translational Research
Chandan Guha, MD, PhD
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, NY-10461
718-430-3550/FAX 781-231-5064
cguhamd@gmail.com

Quality of Life
Lisa Kachnic, MD
Columbia University Medical Center/Herbert Irving
Comprehensive Cancer Center
Department of Radiation Oncology
622 West 168th Street
New York, NY 10032
212-305-9987
lak2187@cumc.columbia.edu

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

Statistician
Kathryn Winter, MS
NRG Oncology
50 South 16th Street, Suite 2800
Philadelphia, PA 19102
215-574-3198/FAX 215-928-0153
winterk@nrgoncology.org

Pathology
Jining Feng, MD, PhD
Beaumont Hospital, Royal Oak
3601 W 13 Mile Rd
Royal Ok, MI 48073
248-898-9060
jining.feng@corewellhealth.org

Alliance
Eileen O'Reilly, MD
Memorial Sloan- Kettering Cancer Center
300 East 66th Street, Office 1021,
New York, NY 10065
646-888-4182/FAX 646-888-4255
oreillye@mskcc.org

ECOG-ACRIN
Dr. A. Bapsi Chakravarthy, MD
Vanderbilt-Ingram Cancer Center
2220 Pierce Avenue, B-1034A
Nashville, TN 37232-5671
615-322-2555/FAX 615-343-0161
bapsi.chak@vumc.org

NRG Oncology Contact Information

Data Manager: For questions concerning eligibility or data submission	Wendy Bergantz, RN NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 215-574-3230 BergantzW@NRGOncology.org
RTQA Questions: For questions concerning RT data submission	Susan McNulty, BS, RT(R)(T), CMD IROC Philadelphia – RT QA Center NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102215-940-8907 smcnulty@acr.org

NRG Oncology Contact Information (Continued)

RT Credentialing:	http://irochouston.mdanderson.org OR IROC-Credentialing@mdanderson.org
RT data submission to TRIAD:	Triad-Support@acr.org
Protocol Development:: For questions concerning protocol and informed consent versions & amendments	Kathryn Okrent NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 215-717-0856 okrentk@nrgoncology.org
Gastrointestinal Non-Colorectal Committee Chair:	Christopher Crane, MD

Protocol Agent

Agent	Supply	NSC #	IND #
*Erlotinib	NCI/PMB	718781	
Gemcitabine	Commercial	N/A	Exempt
Capecitabine	Commercial	N/A	Exempt
Fluorouracil	Commercial	N/A	Exempt

Participating Sites (4/26/16)

☐ U.S. Only
☐ Canada Only
☒ U.S. and Canada
☒ Approved NRG International Member Sites

Document History

	Version/Update Date	Broadcast Date
Amendment 10	**January 17, 2024**	**N/A**
Amendment 9	May 4, 2023	N/A
Amendment 8	April 11, 2023	N/A
Amendment 7	April 12, 2018	N/A
Amendment 6	May 12, 2016	June 28, 2016
Update	April 2, 2014	April 2, 2014
Amendment 5	February 19, 2014	April 2, 2014
Amendment 4	June 22, 2012	July 23, 2012
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

NRG Oncology Headquarters
215-574-3189
1-800-227-5463, ext. 4189

CONTACT INFORMATION (17-JAN-2024)		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at http://www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 Submit data electronically via the NRG Oncology/RTOG web site, www.rtog.org Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the study data manager listed on the NRG Oncology contact information table on the protocol cover page.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For imaging data submission questions: IROCimagearchive@acr.org; please include trial number in the email subject line. **For TRIAD access and installation support:** TRIAD-Support@acr.org Triadhelp.acr.org **TRIAD Software Installation:** **https://triadinstall.acr.org/triadclient/**		

The following NCTN Group Study Champions have been added to this trial:
Alliance: Eileen O'Reilly, MD
ECOG-ACRIN: Anuradha Bapsi Chakravarthy, MD
SWOG: Philip A Philip, MD, PhD

TABLE OF CONTENTS

NRG ONCOLOGY

RTOG 0848

A PHASE II-R AND A PHASE III TRIAL EVALUATING BOTH *ERLOTINIB (PHII-R) AND CHEMORADIATION (PH III) AS ADJUVANT TREATMENT FOR PATIENTS WITH RESECTED HEAD OF PANCREAS ADENOCARCINOMA

***(PH II-R ERLOTINIB RANDOMIZATION COMPLETED, ARM 2 CLOSED TO ACCRUAL EFFECTIVE 4/02/14)**

CURRENT SCHEMA (12-APR-2018)

FIRST STEP:
ADJUVANT SYSTEMIC TREATMENT

Note: Up to 3 months of chemotherapy may be initiated prior to registration-refer to Sections 3.1.2 and 7.1.1.

REGISTER

Arm 1:
Gemcitabine alone or combination chemotherapy x 5 months

Arm 2:
Gemcitabine + Erlotinib x 5 cycles
(Arm 2 closed to accrual effective 4/02/14)

Evaluate To Confirm No Progression

SECOND STEP:
RT RANDOMIZATION
For Non-Progressing Patients

If no progression, then:

STRATIFY

Nodal Status:
1. involved
2. uninvolved

CA19-9 Result:
1. ≤ 90
2. > 90 – 180

Surgical Margins:
1. positive (R1)
2. negative (R0)

Adjuvant Systemic Treatment:
1. Gemcitabine alone
2. FOLFIRINOX or mFOLFIRINOX
3. Non-oxaliplatin gemcitabine combinations

RANDOMIZE

Arm 3:
1 month of gemcitabine or combination chemotherapy

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

NRG ONCOLOGY

RTOG 0848

A PHASE II-R AND A PHASE III TRIAL EVALUATING BOTH *ERLOTINIB (PHII-R) AND CHEMORADIATION (PH III) AS ADJUVANT TREATMENT FOR PATIENTS WITH RESECTED HEAD OF PANCREAS ADENOCARCINOMA

***(PH II-R ERLOTINIB RANDOMIZATION COMPLETED, ARM 2 CLOSED TO ACCRUAL EFFECTIVE 4/02/14)**

SCHEMA (2/19/14 to 6/28/16)

FIRST STEP:
ADJUVANT SYSTEMIC TREATMENT

REGISTER

→ **Arm 1:**
Gemcitabine x 5 cycles

Arm 2:
Gemcitabine + Erlotinib x 5 cycles
(Arm 2 closed to accrual effective 4/02/14)

Evaluate to Confirm No Progression

If no progression, then:

SECOND STEP:
RT RANDOMIZATION
For Non-Progressing Patients

STRATIFY

Nodal Status:
1: involved
2: uninvolved

CA19-9 result:
1: ≤ 90
2: > 90 – 180

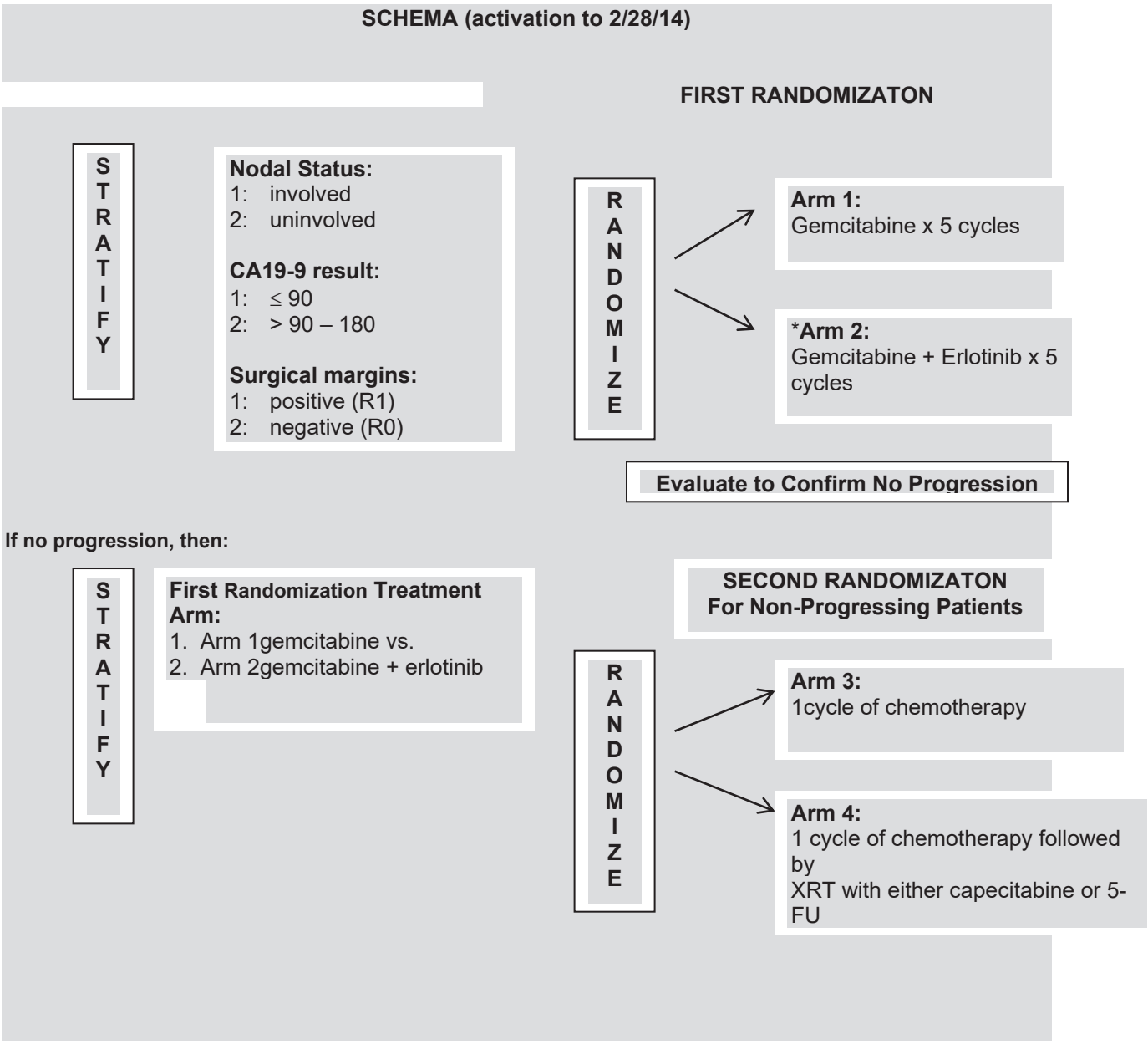
Surgical margins:
1: positive (R1)
2: negative (R0)

RANDOMIZE

→ **Arm 3:**
1cycle of chemotherapy

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

First Randomization Treatment Arm: (For patients registered prior to 4/02/14*)*
1. Arm 1 gemcitabine vs.
2. Arm 2 gemcitabine + erlotinib



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 RT randomization AND completion of first chemotherapy month 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: 545

ELIGIBILITY CHECKLIST—STEP 1 (5/12/15)

NRG Oncology Institution #
RTOG 0848
Case #

_____ (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 pancreatico-duodenectomy.

_____(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 (or within 31 days prior to day 1 of chemotherapy post-surgery for those patients having started chemotherapy prior to first step registration)?

_____(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 and prior to any systemic treatment?

_____(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 any prior systemic chemotherapy for the study cancer other than up to 3 months of the acceptable agents noted in section 3.2.3?

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

(Continued on next page)

NRG Oncology Institution #
RTOG 0848
Case #

_____(N) 15. Does the patient have coexistent medical condition that would preclude protocol therapy (as outlined in Section 3.2)?

_____(N) 16. Is the patient pregnant or lactating?

_____(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 prior to registration for patients who have not received any chemotherapy OR ≥ 2 years prior to the first day of chemotherapy for patients having started chemotherapy.?

_____(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. Is the interval between definitive tumor-related surgery and 1st step registration between 21-70 days for patients who have not received any chemotherapy OR between 21-77 days for patients entering the study who have already received up to 3 months of adjuvant chemotherapy as per the treating institution?

_____(Y/N) 22. Has the patient received up to 3 months of chemotherapy at the time of registration for his/her pancreatic cancer?

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)

_____ 6. Verifying Physician

_____ 7. Patient's ID

NRG Oncology Institution #
RTOG 0848
Case #

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

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

_____ 14. Method of payment

_____ 15. Any care at 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)?

NRG Oncology Institution #
RTOG 0848
Case #

_____(N/Y/NA) 26. For patients who have not started chemotherapy prior to study entry, has patient consented to take part in the quality of life study

(Note: Due to the QOL hypothesis, as of the amendment to allow chemotherapy to start before study entry, QOL is not available for patients who have started chemotherapy prior to study entry.)?

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/NRG Oncology audit.

Completed by _____ Date _____

ELIGIBILITY CHECKLIST STEP 2 REGISTRATION (A2)
(5/12/16)

NRG Oncology Institution #
RTOG 0848
Case #

_____ 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 month 1st step: adjuvant systemic treatment
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 (For patients registered prior to 4/02/14)
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? (5/12/16)

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 RT randomization (-/+ fluoropyrimidine sensitized radiotherapy) will occur after the first 5 months of adjuvant systemic therapy.** Patients will be randomized to receive either one additional month of systemic therapy *or* one additional month of systemic therapy followed by chemoradiation. Radiation will be initiated within 21 days of the last treatment of adjuvant systemic therapy. 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 NRG Oncology radiation oncologists Drs. Ross Abrams and William Regine.

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 LAP 07 Trial: The Decision to Evaluate The Effect of Erlotinib in a Phase IIR Analysis (2/19/14)

The addition of erlotinib to gemcitabine for patients with locally advanced pancreatic cancer was recently reported in the LAP 07 trial (Hammel, 2013). In this trial, 442 patients with locally advanced pancreatic cancer were first randomized to gemcitabine alone or gemcitabine plus erlotinib (100 mg/day) for 4 months. Patients without progression were then randomized to 2 additional months of chemotherapy or chemoradiation. After a median follow-up of 36 months, 221 deaths had occurred allowing the planned interim analysis. When analyzed by the initial randomization to gemcitabine alone versus gemcitabine plus erlotinib, the median survival was 13.6 months versus 11.9 months respectively, p =.09, favoring gemcitabine alone. There was an increase in grade 3 diarrhea in the erlotinib arm (p=0.005). Given these results in locally advanced pancreatic cancer, the decision was made to change the evaluation of the effect of erlotinib in RTOG 0848, an adjuvant pancreatic cancer population, to a randomized phase II (Ph II-R) design.

1.5 Decision To Allow Trial Entry After Up To 3 Months of Chemotherapy With Single-Agent Gemcitabine or Combination Chemotherapy (5/12/16)

A primary objective of this trial is to determine the role of radiation after completion of systemic chemotherapy. To facilitate accrual to answer this question, up to 3 months of systemic chemotherapy may be administered prior to study registration. Single-agent gemcitabine, or combination regimens such as gemcitabine/abraxane, and fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFIRINOX), as per institutional standard of care may be utilized. We acknowledge that institutional policies may modify FOLFIRINOX (Conroy 2011), such as reducing irinotecan dosage or omitting the bolus of 5-FU, or other published combination regimens such as gemcitabine and nab-paclitaxel, (Von Hoff 2013) with respect to timing and precise doses. Therefore, single-agent gemcitabine, or combination regimens that include gemcitabine, nab-paclitaxel, oxaliplatin, fluoropyrimidine, or irinotecan, will be allowed.

1.6 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.

1.7 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).

1.8 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).

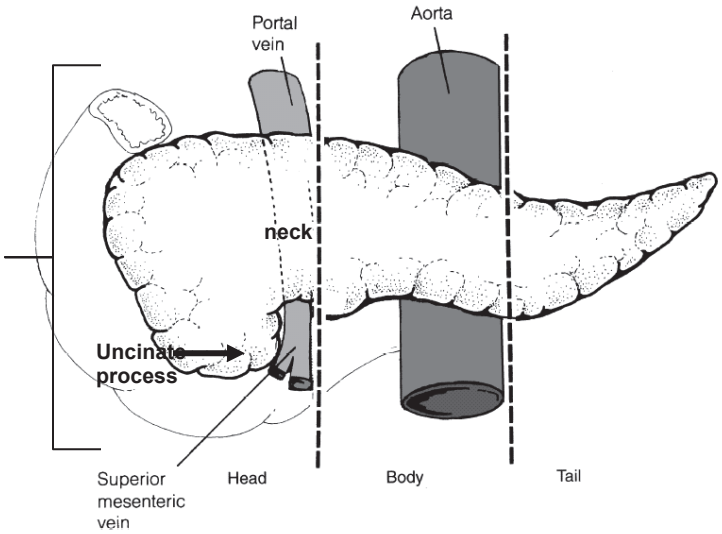


Fig. 18.1. Tumors of the head of the pancreas are those arising to the right of the superior mesenteric–portal vein confluence.

(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.

1.8.1 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.

1.9 Requirement for clear designation of tumor margin status (5/12/16)

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 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.

1.10 Quality of Life/Patient-Reported Outcomes

1.10.1 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.

1.10.2 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.

1.10.3 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 (2/19/14)

(**NOTE**: Ph II-R Erlotinib randomization completed, Arm 2 closed to accrual effective 4/02/2014)

2.1 Primary Objectives (5/12/16)

2.1.1 Ph II-R: To determine whether the addition of erlotinib to gemcitabine adjuvant chemotherapy shows a signal for improved 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 Ph III:To determine whether the use of concurrent fluoropyrimidine and radiotherapy following adjuvant gemcitabine based chemotherapy or non-gemcitabine based chemotherapy such as modified FOLFIRINOX further enhances survival for such patients who are without evidence of progressive disease after 5 months of adjuvant chemotherapy.

2.2 Secondary Objectives (5/12/16)

(**NOTE:** Ph II-R, Erlotinib randomization completed, Arm 2 closed to accrual effective 4/02/14)

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 months 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 adverse events with and without erlotinib for patients with resected head of pancreas adenocarcinoma.

2.2.4 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.

2.2.5 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.

2.2.6 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 (2/19/14)

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

3.1 Conditions for Patient Eligibility (5/12/16)

For questions concerning eligibility, please contact the study data manager.

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 For patients who have not started their chemotherapy prior to registration, the interval between definitive tumor-related surgery and 1st step registration must be between 21-70 days. For patients entering on the study who have already received up to 3 months of adjuvant chemotherapy as per the treating institution, the interval between definitive tumor-related surgery and day one of adjuvant chemotherapy must have between 21-77 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 IV).

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 (or within 31 days prior to day 1 of chemotherapy post-surgery for those patients having started chemotherapy prior to first step registration).

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 (or within 21 days prior to day 1 of chemotherapy post-surgery for those patients having started chemotherapy prior to first step registration), with adequate bone marrow function defined as follows: Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3
- Platelets ≥ 100,000 cells/mm3
- 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 AND prior to any systemic treatment

- **3.1.10** Patients must have: Serum total bilirubin ≤ twice the institutional upper limit of normal within 21 days of registration on study (or within 21 days prior to day 1 of chemotherapy post-surgery for those patients having started chemotherapy prior to first step registration).
- Creatinine levels ≤ twice the institutional upper limit of normal within 21 days of registration on study (or within 21 days prior to day 1 of chemotherapy post-surgery for those patients having started chemotherapy prior to first step registration).
- SGOT must be ≤ 2.5 x the institutional upper limit of normal within 21 days of registration on study (or within 21 days prior to day 1 of chemotherapy post-surgery for those patients having started chemotherapy prior to first step registration).

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 is preferred. Abdominal CT alone is acceptable only if insurance restrictions are experienced. Chest CT/x-ray (CT of chest preferred) within 31 days of registration on study (or within 31 days prior to day 1 of chemo post-surgery for those patients having started chemotherapy prior to first step registration). 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 (5/12/16)

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.: Patients with tumors that are largely intraductal papillary mucinous neoplasms (IPMN) with a minimal or minor component of invasive carcinoma are not eligible. Patients with acinar carcinomas are not eligible. Patients with IPMN's that contain some secondary (minor) foci of adenocarcinoma are also not eligible.

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

3.2.3 Patients entering on the study after pancreaticoduodenctomy, who have not already started chemotherapy must not have had prior systemic chemotherapy for pancreas cancer; note that prior chemotherapy for a different cancer is allowable.

For patients entering on the study who have already received up to 3 months of adjuvant chemotherapy as per the treating institution, patients must not have received adjuvant chemotherapy with agents other than gemcitabine, nab-paclitaxel, oxaliplatin, fluoropyrimidine, or irinotecan for the current pancreatic cancer. 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 (or first day of chemotherapy for patients having started chemotherapy prior to first step registration). Patients with a previous history of carcinoma *in situ* are eligible.

3.2.6 Severe, active co-morbidity, defined as follows per time points indicated below (or per time points indicated below prior to the first day of chemotherapy for patients having started chemotherapy prior to first step registration):

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the 3 months of study registration
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

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 (5/12/16)

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

4.1.1 Glucose and Na, K, Cl, CO2, BUN within 21 days of study entry or within 21 days prior to day 1 of chemotherapy post-surgery for patients having started chemotherapy prior to first step registration

4.2 Highly Recommended Evaluations/Management

4.2.1 If patient consents, a tumor tissue block containing normal tissue and peripheral blood that was obtained prior to treatment submitted for correlative studies is highly recommended. (**NOTE**: Tissue block that includes normal tissue is encouraged).

4.2.2 If patient consents, urine specimen prior to protocol therapy.

4.2.3 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 AND STUDY ENTRY PROCEDURES (17-JAN-2024)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval) or consenting/treating/drug shipment investigator in OPEN must be rostered at the enrolling site with a participating organization.

For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov .

5.1 This study incorporates a two-step registration process and both steps must be completed for all patients. (5/12/16)

Step 1 of registration entails OPEN registration as detailed in Section 5.6, at which time the patient will be assigned to Arm 1 (gemcitabine alone or combination chemotherapy per institutional standard). Note: Chemotherapy may be initiated up to three months prior to registration-refer to Sections 3.2.3 and 7.1.1

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

Patients that have not progressed and have started the 5th month 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 (4/02/14)

In order to be eligible to enroll patients onto this trial, the center must be credentialed for either 3D-CRT or IMRT.

As a first step in the credentialing procedure, a Facility Questionnaire must be completed by all institutions entering patients on this protocol. Update your online electronic Facility Questionnaire, available on the Imaging and Radiation Oncology Core (IROC) Houston web site at http//irochouston.mdanderson.org.

A Credentialing Status inquiry form must be completed. Complete this form on the IROC Houston website above to determine if your site has met all of the requirements. This will be completed in place of updating the previous Facility Questionnaire. When the requirements are met the site and NRG will be notified. NRG will then update the RSS database.

5.3 Pre-Registration Requirements for IMRT Treatment Approach (4/02/14)

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 IROC Houston web site at http://irochouston.mdanderson.org;select “Credentialing” and “Credentialing Status Inquiry”. Instructions for requesting and irradiating this phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select “Credentialing” and “RTOG”.

The institution or investigator must update or complete a Facility Questionnaire (available on the IROC Houston web site at http://irochouston.mdanderson.org) Phantom Irradiation also must be completed for IMRT credentialing. 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 IROC Houston must be successfully completed. 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.

IROC Houston QA Center will notify the institution when all requirements have been met and the institution is RT credentialed to enter patients onto this study. Subsequently, NRG Headquarters will update RSS at CTSU.

5.4 Digital RT Data Submission Using TRIAD (12-APR-2018)

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account, and be registered as an AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- To submit images, the site physics user must be on the site's affiliated rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP IAM account username and password and RCR registration.

If you have any questions regarding this information, please send an email to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.5 Regulatory Pre-Registration Requirements (11-APR-2023)

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support System Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network

(NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or

- Click on the By Lead Organization folder to expand, then select *NRG* and protocol number RTOG-0848.

- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

5.5.2 Requirements For RTOG 0848 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process. (Only add if RT modality credentialing is part of the study design.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Non-English Speaking Canadian and Non-North American Institutions:
Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.5.3 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

Prior to clinical trial commencement, Canadian institutions must also complete and fax (215-569-0206) or e-mail (CTSURegulatory@ctsu.coccg.org) to the CTSU Regulatory Office:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.5.4 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS

*For institutions that **do not have an approved LOI** for this protocol:*
International sites must submit an LOI to NRG Oncology to receive approval to participate in this trial. (For studies involving PMB drug: Prior to granting approval, NRG Oncology will contact CTEP regarding drug availability and shipment. If CTEP approves, NRG Oncology will provide written approval and at that time the institution may seek approval from its local ethics committee). For more details see link below: http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx

*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.

5.6 Registration (12-APR-2018)

5.6.1 OPEN Registration Instructions

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctep core.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

6.0 RADIATION THERAPY (5/12/16)

(NOTE: Ph II-R Erlotinib randomization completed, Arm 2 closed to accrual effective 4/02/14)

NOTE: This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. *PRIOR TO ENROLLING PATIENTS*, see Section 12.2 for information on installing TRIAD for submission of digital RT data

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

For ARM 4 ONLY: radiation therapy begins after 2nd step registration and post completion of additional adjuvant systemic therapy after RT 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 adjuvant systemic therapy after RT 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 adjuvant systemic therapy
b. Only patients who started the 5th month of l adjuvant systemic therapy will be allowed to be randomized to Arm 4 and receive radiotherapy on this protocol.
c. After completion of 5 months of adjuvant systemic therapy, (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 month 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 RT randomization for patients randomized to Arm 4 in order to complete the pre-treatment review process as stated below.
e. TIMELY (within 14 to 21 days after RT randomization) digital submission of treatment planning data (CT planning showing relevant targets, isodose lines, complete volumetric data set DVH) via TRIAD 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 ≥ 6MV beam is required. Use of Tomotherapy is allowed.

6.3 Localization, Simulation, and Immobilization (3D Conformal and IMRT) (5/12/16)

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 month 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.

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).

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:

2.0 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.

3.0 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.

The preoperative tumor (resected GTV)

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.

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.

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) (5/12/16)

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

Critical Structures

NOTE: All required structures must be labeled for digital RT data submission as listed in the table below. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

Standard Name	Description
Preop_GTV	Designation of the preoperative location of the GTV
CVT_5040	
PTV_5040	
Kidney_L	Left Kidney
Kidney_R	Right Kidney
Kidneys	Both Kidneys
Liver	Liver
SpinalCord	Spinal Cord
Stomach	Stomach
External	External patient contour
SmallBowel	Small Bowel
PancJejuno	Pancreatic jejunostomy (used for CTV construction
PancJejuno_CTV	Expansion for inclusion in CTV
V_Portal	
V_Portal_CTV	Expansion of Portal Vein for inclusion in CTV
A_Aorta	Portion of Aorta to be included in Target
A_Aorta_CTV	Expansion of Aorta for inclusion in CTV
A_SupMes	Superior Mesenteric Artery to be included in Target
A_SupMes_CTV	Expansion of Superior Mesenteric Artery for inclusion in CTV
A_Celiac	Portion of Celiac Artery to be included in Target
A_Celiac_CTV	Expansion of Celiac Artery for inclusion in CTV

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

AP/PA with Right and Left Lateral beams.

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.

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 (2/19/14)

6.9.1 Digital Submission of RT Planning Data

For ARM 4 ONLY: radiation therapy begins after 2nd step registration and post completion of additional adjuvant systemic therapy. 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 adjuvant systemic therapy after RT randomization.

Submit via TRIAD (Image Guided Therapy Center) within 14 to 21 days from RT 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)

All RT plans will be digitally submitted via TRIAD for pre treatment review and APPROVAL between 14 to 21 days from RT 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 RT step randomization	Within 3 business days from receipt at IROC Philadelphia	* Within 3-4 business days from RT plan review	* Within 3 business days of resubmission of RT plan
	Submit RT plan digitally via TRIAD 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

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.

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

Doses to PTV and CTV (Per Protocol Limits)

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).

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 Acceptable 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

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

Critical 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 SmallBowel	Max dose ≤ 56 Gy; D15% ≤ 50Gy (no more than 15% of the organ can receive more than 50Gy)
SpinalCord	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 (5/12/16)

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 NRG Oncology radiation oncologists.

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

7.1 First Step: Adjuvant Systemic Treatment (5/12/16)

7.1.1 For patients entering on the study who have not received any protocol chemotherapy, chemotherapy must start within 7 days after registration and must be administered within 72 hours (+/- 3 days) of the scheduled date for these therapies.

For patients entering on the study who have already received up to 3 months of adjuvant chemotherapy, as per the treating institution, with the plan to receive a total of 5 months of adjuvant chemotherapy prior to Step 2 randomization, and have received either single-agent chemotherapy or combination chemotherapy that includes gemcitabine, nab-paclitaxel, oxaliplatin, fluoropyrimidine, or irinotecan, the subsequent month of chemotherapy should begin within 14 days of step 1 registration. (Step 1 registration must occur prior to the start of the fourth month of adjuvant therapy.)

ARM 1

Gemcitabine or allowable combination chemotherapy	Delivered per institutional standard for a total of 5 months Note: Chemotherapy may be initiated prior to registration- refer to Sections 3.2.3.

ARM 2 (**NOTE:** Ph II-R Erlotinib randomization completed, Arm 2 closed to accrual effective 4/02/14). Patients randomized to erlotinib prior to 4/02/14 will continue erlotinib treatment per the protocol.

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 month of chemotherapy to be eligible for the RT randomization. 2nd step registration must be completed for patients with progressive disease by radiographic studies after adjuvant systemic 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 Step: RT Randomization Treatment: (5/12/16)
Referral to radiotherapy for re-evaluation and treatment planning should be done within 7 days of the RT randomization for patients randomized to Arm 4 in order to complete the pre-treatment review process as stated in Section 6.

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

7.2.2 Initiation of the 6th month for Arms 3 and 4 (6th month of systemic treatment) must occur within 4 weeks of the completion of the 5th month of chemotherapy and must be administered within 72 hours (+/- 3 days) of the scheduled date for these therapies.

ARM 3

Gemcitabine or allowable combination chemotherapy	1 month identical to the adjuvant systemic treatment

ARM 4

Gemcitabine or allowable combination chemotherapy	1 month identical to the adjuvant systemic treatment
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(5/12/16)

To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure for comprehensive pharmacologic and safety 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 NRG Oncology 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.

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.

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%.

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

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.

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.

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.

Comprehensive Adverse Events and Potential Risks

Comprehensive Adverse Events and Potential Risks list (CAEPR) for OSI-774 (erlotinib, 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 Specific Protocol Exceptions to Expedited , July Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3622 patients.* Below is the CAEPR for OSI-774 (erlotinib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, July 24, 2013[1]

Adverse Events with Possible Relationship to OSI-774 (erlotinib) (CTCAE 4.0 Term) [n= 3622]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis (Gr 2)***
	Dry eye		***Dry eye (Gr 2)***
	Eye disorders - Other (eyelash in-growth and/or thickening)		
		Eye disorders - Other (corneal perforation)	
		Keratitis	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Gastrointestinal hemorrhage[2]		
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Skin infection[4]		***Skin infection[4] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***

		Intracranial hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
	Pneumonitis		***Pneumonitis (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Nail loss		***Nail loss (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***

[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 includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

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

Also reported on OSI-774 (erlotinib) trials but with the relationship to OSI-774 (erlotinib) 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: OSI-774 (erlotinib) 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: OSI-774 (erlotinib)-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 OSI-774 (erlotinib) in patients with baseline hepatic impairment.

7.3.8 Supply

Erlotinib will be supplied free of charge for this study by NCI.
Drug provided free of charge as part of a research protocol must be used only for the intended study. It is the responsibility of the Investigator to ensure the provided/investigational product is only dispensed to eligible study patients

7.3.9 Accountability

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

Accountability and Supply

This study will be conducted under an NCI/Pharmaceutical Management Branch (PMB) IND. The study agent erlotinib and the associated Investigator Brochure will be provided by PMB.

The Principal Investigator (or authorized designee listed by the Investigator on the site's most recent Supplemental Investigator Data Form [IDF] on file with the PMB) at each participating institution may request erlotinib from NCI's Pharmaceutical Management Branch (PMB). The updated version (11/10/03) of each institution's Drug Authorization Review and Tracking System (DARTS) will require selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the Investigator during the annual Investigator registration process. This process must be completed before a drug order can be entered for that investigator. Any changes to this information will require updating the first two pages of the IDF, having the Investigator sign the revised IDF, and returning it to the PMB via fax at 240-276-7893. Questions about the process should be directed to the PMB at 240-276-6575. Monday through Friday from 8:30 am–4:30 pm Eastern Time. PMB policy requires that drug be shipped directly to the institution where the patient is to be treated.

PMB does not permit the transfer of agents between institutions unless prior approval from PMB is obtained. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to the OAOP application and the associated training guide is available at the following link: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password.
For questions about drug orders, transfers, returns, or accountability, call 240-276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or e-mail PMBAfterHours@mail.nih.gov anytime.

7.3.10 Investigator Brochure

The Investigator Brochure (IB), if available, for this drug will be supplied by the PMB/NCI. All requests for IBs should be e-mailed to ibcoordinator@mail.nih.gov <mailto:ibcoordinator@mail.nih.gov> or the IB Coordinator may be contacted at 240-276-6575. . 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. NRG Oncology applies these policies to all provided drug.

7.4 Gemcitabine HCl (5/12/16)

Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

Supply

Gemcitabine is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption

7.5 Capecitabine (5/12/16)

Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

Supply

Capecitabine is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption

7.6 Fluorouracil (5/12/16)

Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

Supply

Commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption

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 (5/12/16)

7.8.1 Dose Modifications for Erlotinib

NOTE:(Ph II-R Erlotinib randomization completed, Arm 2 closed to accrual effective 4/02/14*)*

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.**

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			

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.

7.8.2 Dose Modifications for Fluorouracil or Capecitabine and Radiation

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 or capecitabine		

Non-Hematologic Toxicity

Only toxicities related to treatment require dose modifications. For patients experiencing 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 (5/12/16)

The medical oncology co-chairs will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy for the gemcitabine versus gemcitabine plus erlotinib research question in this trial. Drs. Safran and Philip, 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 NRG Oncology. 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 NRG Oncology. 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 NRG Oncology, whichever occurs first. Medical oncology reviews need to be completed prior to presenting/publishing the primary endpoint results.

7.10 Adverse Events (12-APR-2018)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.10.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.10.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.11 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.11. **Contact the CTEP-AERS Help Desk if assistance is required**

Definition of an SAE: Any adverse drug even (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, 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.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner

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

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.11 CTEP-AERS Expedited Reporting Requirements (5/12/16)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site
https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to both the NCI at 301-230-0159 and the NRG Oncology dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 trials as described in the table below. Important: All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention 1, 2 (Arm 2)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

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

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

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

Any Phase Study Utilizing a Commercial Agent[1] (Arms 1 and 3)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

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

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

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

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

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day		24-h/5 day	24-h/5 day

Expedited AE reporting timelines are defined as:

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

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

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

- Unexpected Grade 4 and all Grade 5 AEs

Any Phase Study Utilizing Radiation Therapy (including chemoRT studies)[1] (Arm 4)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

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

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

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

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 3 adverse events

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

Exceptions to CTEP-AERS 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 NRG Oncology. Dr. Berger will then perform the next reviews on a quarterly basis when complete data has been received at NRG Oncology.

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 IV). 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

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 IV).

Final Pathology Report

The pathology report must contain all of the elements as outlined in the CAPS guidelines (Appendix IV). 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 (2/19/14)

10.1 General Information

Tumor block, peripheral blood and urine submission are highly recommended to be submitted at study entry. (**NOTE**: Tissue block that contains normal tissue submission is

encouraged). These specimens are to be submitted to the NRG Oncology Biospecimen Bank 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 NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

10.2 Specimen Collection for Tissue Banking (Highly Recommended) (12-APR-2018)

Specimens are to be collected at baseline in all eligible patients who have consented. These include the tumor tissue block and peripheral blood (plasma and whole blood) and urine. 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.

10.2.1 Tissue Blocks

The following must be provided in order for the case to be evaluable for the NRG Oncology Biospecimen Bank:

- One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide (block) or can be the diagnostic slide itself.)
- A corresponding paraffin-embedded tissue block of the primary tumor (the block must match the H&E being submitted) containing tumor and normal tissue if present **(NOTE: H&E and tissue block that includes normal tissue 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. These must come from the same block as the H&E being submitted. N**OTE**: A kit with the punch tool, specimen tube, and instructions can be obtained from the Biospecimen Bank with frozen specimen kids. To request a kit, contact the Biospecimen Bank at NRGBB@ucsf.edu or 415-476-7864. Block or core must be clearly labeled with the pathology identification number and block ID that corresponds to the submitted Pathology Report.
  See Appendix V for specimen punch tool kit and instructions.
- A Pathology Report documenting that the submitted block or core contains tumor and the clinical status. The report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The date of procedure and surgical pathology report numbers and information must NOT be removed from the report.
- A Specimen Transmittal Form (ST) clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's NRG Oncology case number.

10.2.2 Whole Blood, Plasma, and Urine (Highly Recommended)

- 5 cc of whole blood, and 7-10cc of blood to be separated for plasma are required.
  See Appendix V for blood collection kit, processing and shipping instructions.
- 10mL urine to be collected at study entry.
  See **Appendix V** for urine collection kit, processing and shipping instructions.
- A Specimen Transmittal Form (ST) documenting the date of collection of the whole blood, plasma, and urine; the NRG Oncology protocol number, the patient's NRG

Oncology case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

NOTE: At the time of progression, if a biopsy is obtained to document progression, it is highly recommended that an H&E and a block of the tumor tissue be sent to NRG Oncology Biospecimen Bank. In addition peripheral blood (10 cc) is also requested at the time of progression. See Section 10.4 (Specimen Collection Summary table)

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 the ST Form the storage conditions used and time stored.

10.4 Specimen Collection Summary (12-APR-2018)

Highly Recommended Specimens			
Specimens taken from patient:	Collected When:	Submitted as:	Shipped:
Representative H&E stained slides of the primary tumor	Removed at time of surgery	H&E Slide (slide can be a duplicate cut stained H&E or the diagnostic slide.)	Ambient to NRGBB-SF
1 corresponding block primary tumor containing normal tissue **(NOTE**: A tissue block containing normal tissue is not mandatory but is encouraged) OR 5mm punch of tumor tissue block with 25 unstained sections on plus slides.	Removed at time of surgery	Preserved in formalin; paraffin embedded. Note: The block, punch and unstained must be taken from same block as the H&E slide being submitted	Ambient. (A cold pack is recommended during warmer months) to NRGBB-SF
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Prior to chemotherapy start, if possible, otherwise, at study entry	Frozen plasma samples containing minimum of 0.5 mL per aliquot in 1 mL cryovials (five) Store frozen at -80°C	Plasma sent frozen on dry ice via overnight carrier to NRGBB-SF
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 , (purple/lavender top tube) and mix	Prior to chemotherapy start, if possible, otherwise, at study entry . Note: If site missed this collection time point they may collect whole blood for DNA at a later time point instead but must note	Frozen whole blood samples containing of 1.5 mL per aliquot in 2 mL cryovials (three)	Whole blood sent frozen on dry ice via overnight carrier to NRGBB-SF

	this on the ST Form.		
10-25 mL clean-catch urine	Prior to chemotherapy start, if possible, otherwise, at study entry	One 10 mL urine aliquot in one sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20° C (short term only) or 80° C	Urine sent frozen on dry ice via overnight carrier to NRGBB-SF
Representative H&E stained slides of the progression tumor	Disease progression	H&E Slide (slide can be a duplicate cut stained H&E, or the diagnostic slide.)	Ambient to NRGBB-SF
1 block progression tumor OR punch of block plus 25 unstained sections on plus slides.	Disease progression	Preserved in formalin; paraffin embedded. Block or punch/unstained must come from same block as H&E being submitted	Ambient. (A cold pack is recommended during warmer months to NRGBB-SF
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 to NRGBB-SF
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube#2, (purple/lavender top) and mix	Disease progression	Frozen whole blood samples containing 1.5 mL per aliquot in 2 mL cryovials (three)	Whole blood sent frozen on dry ice via overnight carrier to NRGBB-SF

10.5 Submit materials as follows: (12-APR-2018)

US Postal Service Mailing Address: <u>For Non-frozen Specimens Only</u>
NRG Oncology Biospecimen Bank
University of California San Francisco-Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143

Courier Address (FedEx, UPS, etc.): <u>For ALL Frozen Specimens and Trackable FFPEs</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476- 7864/FAX 415-476-5271;
NRGBB@ucsf.edu

10.6 Reimbursement (2/19/14)

Please note that with the start of the new NCI National Clinical Trials Network (NCTN) Program, NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study,

which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.7 Confidentiality/Storage (4/02/14)

(See the 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 NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.7.2 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.

11.0 PATIENT ASSESSMENTS (2/19/14)

11.1 Study Parameters: See Appendix I.

11.2 Evaluation for Progression following Adjuvant Systemic Therapy

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 1st step adjuvant systemic therapy but prior to clinical evaluation for progression, as well as at 9, 12, and 24 months from start of 1st step adjuvant systemic 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:

NRG Oncology*
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 (5/12/16)

Item	Due
Demographic Form **(A5)**	**Within 2 weeks of 1st step registration**
Initial Evaluation Form **(I1) (for patients who have not received chemotherapy prior to registration**	
Initial Evaluation Form **(I2)** (for patients having started chemotherapy prior to first step registration)	
Slides/Blocks **(P2)**	
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 1st step adjuvant systemic therapy but prior to clinical evaluation for progression, and then at 9, 12, and 24 months from the START OF 1st step adjuvant systemic therapy
Post Adjuvant Systemic Treatment tumor status form **(F3)**	1 week after evaluation for disease progress post 1st step adjuvant systemic treatment
Adjuvant Systemic Treatment Form **(TF)** **(For patients registered prior to amendment 6 only)**	1 week after completion of 1st step adjuvant systemic treatment
Arm 3 or 4 1st cycle Treatment Form **(AT)** **(For patients registered prior to amendment 6 only)**	1 week after completion of 1st cycle Arm 3 or 4 treatment
Systemic Treatment Summary Form (TC)	1 week after completion of month 5 treatment

(For patients registered to amendment 6 version of the protocol)	
Additional Systemic Treatment Form (AX) **(For patients registered to amendment 6 version of the protocol)**	1 week after completion of month 6 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)** **FOR PATIENTS WHO DO NOT RECEIVE ARM 3 OR 4 TREATMENT**	Every 6mo x 2 then annually
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 NRG Oncology ONLY if specifically requested.

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.4 for account access and installation instructions) ARM 4 ONLY (5/12/16)

Item	Due
Preliminary Dosimetry Information (DD)	
Digital Data Submission – Treatment Plan along with pre and post-operative CT scans submitted to TRIAD exported from treatment planning machine by Physicist	Within 7-14 days post 1st chemo month after RT randomization
Digital data submission includes the following and must be submitted for plan approval pre-RT start:	
• CT data, 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 • All required structures **MUST** be labeled per the table in Section 6.5. • *The "RTOG 0848Datasheet" is available in the Forms section of the of the NRG Oncology/RTOG web* site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0848 Submit via TRIAD with the digital data listed above.	
Upon submission of the digital data via TRIAD, complete an online digital data transmission form (DDSI) located in the Core Lab Tab at http://www.rtog.org/CoreLab/TRIAD.asp	

NOTE: All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.	
Final Dosimetry Information Radiotherapy Form **(T1) [copy to HQ]** Daily Treatment Record **(T5) [copy to HQ]**	Within 1 week of RT end
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	

13.0 STATISTICAL CONSIDERATIONS (2/19/14)

13.1 Endpoint(s)

13.1.1 Primary Endpoints

Ph II-R: For the erlotinib question (first randomization closed to accrual 4/02/14): Overall survival (OS) (failure: death due to any cause)

Ph III: 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 (Ph II-R) and the chemoradiation question (Ph III) unless otherwise noted

- Disease-free survival (failure: local or regional disease progression, distant metastases, second primary, or death due to any cause)
- Adverse events
- Pre-op imaging to determine frequency of objective criteria of resectability
- Quality of Life: fatigue as measured by the FACIT-F (primary) and the PROMIS derived short form (exploratory)

13.2 Stratification (5/12/16)

13.2.1 Current Stratification

Prior to the chemoradiation 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). Patients entered prior to the closure of the erlotinib randomization (4/02/14) will also be stratified by their first treatment (gemcitabine vs. gemcitabine + erlotinib). As of the amendment to allow induction chemotherapy regimens beyond single-agent gemcitabine (Amendment 6), patients are also stratified by chemotherapy (single-agent gemcitabine vs gemcitabine combination).Patients must start the 5th month of chemotherapy to be eligible for the chemoradiation randomization. The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution. [Zelen, 1974]

13.2.2 Previous Stratification

During the period when there was an erlotinib randomization in addition to the chemoradiation randomization, patients were stratified as follows. Prior to the erlotinib randomization, patients were stratified with respect to the following stratification variables: nodal status (involved vs. uninvolved), serum CA19-9 (≤ 90 vs. > 90-180), and chemotherapy (single agent gemcitabine versus combination chemotherapy at any time), and surgical margins (positive vs. negative). Prior to the chemoradiation randomization, patients were stratified with respect to the following stratification variable: first treatment (gemcitabine vs. gemcitabine + erlotinib). Patients had to start the 5th cycle of chemotherapy to be eligible for the chemoradiation randomization. The treatment

allocation scheme described by Zelen was used because it balances patient factors other than institution. [Zelen, 1974]

13.3 Sample Size and Power Justification (17-JAN-2024)

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 chemotherapy improves overall survival for patients who are without evidence of progressive disease after 5 months of 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 $\alpha = 0.05$
- 80% power
- 3.5 years of follow-up post accrual completion
- Two interim significance tests and a final test are planned

Using the group sequential design method [Pocock, 1977] with 2 interim analyses, 354 randomized patients are required to detect an increase in MST from 17 to 22.5 months [measured from the date of RT randomization (chemotherapy vs. chemotherapy followed by chemoradiation) to the date of death], translating into a hazard ratio (experimental/control) of 0.76. Based on the number of patients that will not proceed to the RT randomization due to progression, death without progression, not starting the 5th month of adjuvant chemotherapy treatment, or refusal, 545 patients will be entered.

Redesign

The redesign was done in accordance with the NCI Policy for Major Design Amendments for Ongoing Randomized Clinical Trials and redesign specifics performed by a statistician independent from the trial.

Due to a lower than expected event rate throughout the trial, and a decreased event rate for the primary endpoint in post 5-year follow-up, definitive analysis based on the requisite events defined in Section 13.4.3 (n= 316 OS events) is projected to occur in 2029 or later. Consequently, the analysis plan is modified to specify conduct of the primary endpoint analysis at the earlier of either a) the requisite events are observed or

b) all patients have achieved a minimum of 5 years of potential follow-up time from enrollment, which will occur in the fourth quarter of 2023.

In the original design, observation of 316 OS events provided statistical power of 80% for testing the specified alternative (34% reduction in failure rate, or HR=0.76) at one-sided alpha 0.05. At the current event rate, it is projected that 316 OS events may not be reached before 2029. By October 1, 2023, it is anticipated that at least 265 events will have been observed. Undertaking analysis at this fixed calendar time will result in a modest decrease of statistical power for the primary endpoint as follows:

# Events	Statistical Power
265	0.72
295	0.76

13.3.2 (4/02/14). The study design for the erlotinib research question has been revised to a Ph II-R design. The primary hypothesis for the Ph II-R portion is that the addition of erlotinib to standard adjuvant gemcitabine will show a signal for an increase in overall survival for patients with resected head of the pancreas adenocarcinoma. A total of 200 events (deaths) between the gem and gem/erlotinib treatment arms will provide 80% power to detect a signal for an increase in median overall survival from 22 to 28.8 months and 90% power to detect a signal for an increase in median overall survival from 22 to 30.6 months (HRs of 1.31 and 1.39 respectively, in favor of the erlotinib arm) with the addition of erlotinib and a 1-sided alpha of 0.15. The number of patients accrued prior to this amendment is sufficient to obtain the 200 required events with a projected analysis timeline of ~ 2.5 years from the amendment.

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 (11-APR-2023)

(4/02/14) 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

Chemoradiation Question Primary Endpoint: Overall Survival

Two 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 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

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 NRG Oncology 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

Erlotinib Question (First Randomization) Primary Endpoint: Overall Survival

The primary hypothesis of the erlotinib question is whether the addition of erlotinib will show a signal for an increase in overall survival (potential effect sizes as described in Section 13.3.2) for patients with resected head of pancreas adenocarcinoma. This major analysis will occur after a total of 200 events (deaths) have occurred between the gem and gem/erlotinib treatment arms. 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, regardless of the amount of erlotinib received, will be included in the comparison and will be grouped in the analysis by assigned treatment from the erlotinib randomization (gemcitabine vs. gemcitabine/erlotinib). The primary hypothesis of treatment benefit will be tested using the log-rank statistic with a significance level of 0.15. 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.

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 at the earlier of either a) the requisite events are observed [316 OS events] or b) all patients have achieved a minimum of 5 years of potential follow-up time from RT randomization - which will occur in the fourth quarter of 2023. 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 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. 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

FACIT-F Scoring and Analysis

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

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).

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.

Analysis for Secondary Endpoints Related to HRQoL

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.

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

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), surgical margins (positive vs. negative) and chemotherapy (single agent gemcitabine versus combination) and timing of study entry (prior to any chemotherapy versus after up to 3 months) 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 NRG Oncology Data Monitoring Committee on a semi-annual basis for accrual (while applicable) and adverse events; as well as for efficacy/futility as specified in Section 13.4.2.

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 (2/19/14)

The primary erlotinib analysis is planned with 200 deaths. 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), it is projected that there will be 180 deaths 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.

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 assessing 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 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 0.025 one-sided test and 180 deaths.

Interaction HR	Power 50:50 split	Power 25:75 split	Power 10:90 split
1.6	0.88	0.77	0.47
1.7	0.94	0.86	0.56
1.8	0.97	0.92	0.65
1.9	0.99	0.96	0.73

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.

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 (12-APR-2018)

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 0.49 for males and 0.40 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	4	5	9
Not Hispanic or Latino	230	306	536
Ethnic Category: Total of all subjects	234	311	545
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	3	3	6
Asian	3	3	6
Black or African American	20	15	35
Native Hawaiian or other Pacific Islander	3	3	6
White	205	287	492
Racial Category: Total of all subjects	234	311	545

REFERENCES (5/12/16)

Abrams, R.A.: Lillemoe, K., Piantadosi, S. Continuing Controversy Over Adjutant Therapy of Pancreatic Cancer, (Commentary on: Adjuvant Chemoradiotherapy and Chemotherapy in Resectable Pancreatic Cancer: A Randomised Controlled Trial, Neoptolemos, J.P., et.al., pp. 1576-1585) The Lancet, 358(9293):1565-1566, 10 November 2001.

Abrams RA, Winter KA, Regine WF, et. al. Correlation of RTOG 9704 (adjuvant therapy of pancreatic adenocarcinoma) radiation therapy quality assurance scores with survival. Journal of Clinical Oncology 2008; 25, 18s Part I: page 203 s (abstract 4523)

Ali S, Almhanna K , Chen W, et al. Differentially expressed miRNAs in the plasma may provide a molecular signature for aggressive pancreatic cancer. Am J Transl Res 2011;3(1):28-47

Baselga J, Rosen N. Determinants of RASistance to anti-epidermal growth factor receptor agents. J Clin Oncol 2008;26:1582-4. PMID 18316790

Bower JE and Bower JE. Prevalence and causes of fatigue after cancer treatment: the next generation of research [comment]. Journal of Clinical Oncology 23(33): 8280, 2005.

Buck E, Eyzaguirre A, Barr S, et al. Loss of homotypic cell adhesion by epithelial-mesenchymal transition or mutation limits sensitivity to epidermal growth factor receptor inhibition. Mol Cancer Ther 2007;6:532-41. PMID 17308052

Burris HA, Moore MJ, Anderson J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403-13. PMID 9196156

Cella D, Lai J-S, Chang C-H, et al: Fatigue in cancer patients compared to that of the general United States population. Cancer 94: 528-538, 2002.

Cella D, Yount S, and Rothrock N. The Patient-Reported Outcomes Measurement Information System (PROMIS) progress of an NIH roadmap cooperative group during its first two years. Medical Care 45: S3-S11, 2007.

Cella D, Lai J, Garcia SF, et al: The Patient Reported Outcomes Measurement Information System--Cancer (PROMIS-Ca): Cancer-specific application of a generic fatigue measure. [Abstract]. Journal of Clinical Oncology, 26, 6537, 2008.

College of American Pathologists (CAP). Standardized Staging of the Exocrine Pancreas. Webpage accessed at www.cap.org/apps on January 6, 2009

Conroy, T, Desseigne F, Yehou M, et al. Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-1825, 2011

Cox DR. Regression models and life tables. J Royal Stat Soc 1972; Series B, v34:187-229, 1972.

Donaldson GW, Moinpour CM. Learning to live with missing quality of life data in advanced-stage disease trials. J Clin Oncol 2005;23:1-5)

Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non- small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 2005:23:5900-9. PMID 16043828

Freidlin B, Korn EL. A comment on futility monitoring. Controlled Clinical Trials 2002;23:355-66.

Garcia SF, Cella D, Clauser SB, et al: Special series (PROACT): Standardizing patient-reported outcomes assessment in cancer clinical trials: A PROMIS initiative. J Clin Oncol 25: 5106-5112, 2007.

Greene FL, Page DL, Fleming ID, et.al. eds. Chpt. 18: Exocrine Pancreas in AJCC Cancer Staging Manual, 6th Ed. Springer Verlag New York 2006. pp 157-164

Griffin JF, Smalley SR, Jewell W, et al. Patterns of failure after curative resection of pancreatic carcinoma cancer 1990;66:56-61. PMID 2354408

Gudjonsson B. Cancer of the pancreas: 50 years of surgery. Cancer 1987; 60:2284-2303. PMID 3326653

Hammel P, Huguet F, Van Laethem JL, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. J Clin Oncol 31, 2013 (suppl; abstr LBA4003)

Hsu CC, Herman JM, Corsini MM, et al. Benefit of adjuvant chemoradiation therapy for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study of 1045 patients. 2008 Gastrointestinal Cancers Symposium. (Abstr 2008)

Jimeno A, Tan AC, Coff J, et al. Coordinated epidermal growth factor receptor pathway gene overexpression predicts epidermal growth factor receptor inhibitor sensitivity in pancreatic cancer. Cancer Res 2008;68:2841-9. PMID 18413752

Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;120:899. PMID 4015380

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Stat Assoc 1958;53:457-81.

Klinkenbijl JH, Jeekel, J, Sahmoud, T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999; 230:776. PMID 10615932

Lai J-S, Cella D, Choi SW, et al: Developing a fatigue item bank from the patient-reported outcomes measurement information system (PROMIS FIB version 1). Presented at the International Conference on Survey Methods in Multinational, Multiregional, and Multicultural Contexts (3MC). June 25-28, 2008. Berlin, Germany.

Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother 1966;Rep 50:163-70.

Moore MJ, Goldstin D, Hamm, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007a;25:1960-5. PMID 17452677

Moore MJ, Cunha Santos G, Kamel-Reid S, et al. The relationship of K-ras mutations and EGFR gene copy number to outcome in patients treated with erlotinib on National Cancer Institute of Canada Clinical Trials Group trial study PA.3. ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007b: 4521.
http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=47&abstractID=33914

Neoptolemos, JP, Dunn, JA, Stocken, DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001; 358:1576. PMID 11716884

Neoptolemos, JP, Stocken, DD, Friess, H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004; 350:1200. PMID 15028824
Neuhaus, P, Riess, H, Post, S, et al. CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine vs. observation in patients with resected pancreatic cancer (abstract). J Clin Oncol 2008; 26:1009s.

Nitecki SS, Sarr MG, Colby TV, et al. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? Ann Surg 1995; 221:59-66. PMID 7826162

Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297:267-77. PMID 17227978

Piorkowski RJ, Blievernicht SW, Lawrence W Jr, et al. Pancreatic and periampullary carcinoma: experience with 200 patients over a 12-year period. Am J Surg 1982;143:189-93. PMID 6174049

Pocock SJ. Group sequential methods in the design and analysis of clinical trials. Biometrika 1977:64:191-9.

Raut CP, Tseng JF, Sun CC, et al. Impact of Resection Status on Pattern of Failure and Survival After Pancreaticoduodenectomy for Pancreatic Adenocarcinoma. Ann Surg. 2007; 246(1): 52–60

Regine WF, Winter KA, Abrams R, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA 2008;299:1019-26. PMID 18319412

Robinson DW, Eisenberg DF, Cella D, et al: The prognostic significance of patient-reported outcomes in pancreatic cancer cachexia. J Support Oncol 6: 283–290, 2008.

Rocha Lima CM, Green MR, Rotche R, et al: Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 22: 3776-3783, 2004.

Shah AN, Summy JM, Zhang J, et al. Development and characterization of gemcitabine-resistant pancreatic tumor cells. Ann Surg Oncol 2007;14:3629-37. PMID 17909916

Staley CA, Cleary KR, Abbruzzese JL, et al. The Need for Standardized Pathologic Staging of Pancreaticoduodenectomy Specimens. Pancreas 2006;12: 373-380

Tepper J, Nardi G, Suit H. Carcinoma of the pancreas: review of MGH experience from 1963-1973. Analysis of surgical failure and its implications for radiation therapy. Cancer 1976;37:1519-24. PMID 1260670

Thiery JP. Epithelial-mesenchymal transitions in development and pathologies. Curr Opin Cell Biol 2003;15:740-6. PMID 14644200

Thomson S, Buck E, Petti F, et al. Epithelial to mesenchymal transition is a determinant of sensitivity of non-small cell lung carcinoma cell lines and xenografts to epidermal growth factor receptor inhibition. Cancer Res 2005; 65:9455-62. PMID 16230409

Von Hoff DD, Ervin T, Arena FP, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine N Engl J Med 2013; 369:1691-1703

Yellen SB, Cella DF, Webster K, et al: Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. Journal of Pain and Symptom Management 13: 63-74, 1997.

Yeo, CJ, Cameron, JL, Sohn, TA, Lillemoe, KD, Pitt , HA, Talamini, MA, Hruban, RH, Ord, SE, Sauter, PK, Coleman, JA, Zahurak, ML, Grochow, LB, and Abrams, RA. Six Hundred Fifty Consecutive Pancreaticoduodenectomies in the 1990s, Pathology, Complications, and Outcomes. Annals of Surgery, 226(3):248-260, 1997.

Zelen M. The randomization and stratification of patients to clinical trials. J Chron Dis 1974; 27:365-75.

APPENDIX I (5/12/16)
STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS

(NOTE: Ph II-R, ERLOTINIB RANDOMIZATION COMPLETED, ARM 2 CLOSED TO ACCRUAL EFFECTIVE 4/02/14)

Assessments	31 days prior to registration for patients who have not started chemotherapy or 31 days prior to day 1 of chemotherapy post surgery	21 days prior to registration for patients who have not started chemotherapy or 21 days prior to day 1 of chemotherapy post surgery	14 days prior to registration for patients who have not started chemotherapy or 14 days prior to day 1 of chemotherapy post surgery
History	X		
Physical with weight and vital signs	X		
Performance Status			X
CT/MRI of abdomen/pelvis	X (See Section 3.1)		
Chest CT or x-ray	X		
CBC w/ diff; platelets & ANC		X	
SGOT; total bilirubin creatinine		X	
Na, K, Cl, CO_2 , glucose, BUN		X	
Post-op CA19-9		X	
Serum pregnancy test (if applicable)			X
Quality of Life Evaluation (*if patient consents)*	Prior to 1st step registration		
Urine submission (*if patient consents)*	Obtained prior to start of chemotherapy if possible, otherwise at study entry		
Tissue and blood, submission *(if patient consents)*	Obtained prior to start of chemotherapy if possible, otherwise at study entry		

APPENDIX I (5/12/16)

STUDY PARAMETER TABLE: DURING TREATMENT ASSESSMENTS

(**NOTE: PH II-R ERLOTINIB RANDOMIZATION COMPLETED, ARM 2 CLOSED TO ACCRUAL EFFECTIVE 4/02/14*)***

Assessments	During 1st step adjuvant systemic therapy per institutional standard	Within 3 weeks after completing the 5th month of 1st step adjuvant systemic therapy	Post 2nd step randomization: Wkly during chemo/RT
Physical with weight and vital signs	X	X	X
Performance Status	X	X	
CT/MRI of abdomen/pelvis		X	
Chest CT or x-ray		X	
CBC w/ diff; platelets & ANC	X	X per institutional standard	X
SGOT; total bilirubin creatinine		X per institutional standard	
Na, K, Cl, CO_2, glucose, BUN		X per institutional standard	
Quality of Life Evaluation (*if patient consents)*	After completion of 1st step adjuvant systemic therapy but prior to CLINICAL EVALUATION FOR PROGRESSION		
Adverse event eval (and as needed based on reporting requirement)	X	X	X

APPENDIX I (5/12/16)
STUDY PARAMETER TABLE: FOLLOW UP ASSESSMENTS

(**NOTE: PH II-R ERLOTINIB RANDOMIZATION COMPLETED, ARM 2 CLOSED TO ACCRUAL EFFECTIVE 4/02/14)**

Assessments	**Following completion of all treatment for patients on Arms 1 and 2 ONLY** Every 6mos x 4yrs, then annually	**Following completion of all treatment for patients on Arms 3 or 4** Every 3mos x 2yrs, Every 6mos x 3yrs, then annually
Physical with weight and vital signs	X	X
Performance Status	X	X
CT/MRI of abdomen/pelvis	X	X
Chest CT or x-ray	X	X
Quality of Life Evaluation (*if patient consents)*	9, 12, and 24 months from the start of 1st step adjuvant systemic therapy	
CA19-9	X	X
Adverse event eval (and as needed based on reporting requirement)	X	X

APPENDIX II
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 III

STAGING FOR PANCREAS
AJCC, 6th Edition

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

MX	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 IV

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

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)**

APPENDIX V (5/12/16)

Appendices for NRG Oncology Biospecimen Collection

NRG Oncology FFPE Specimen Plug Kit Collection
NRG Oncology Blood Collection Kit Instructions
NRG Oncology Urine Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143

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

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

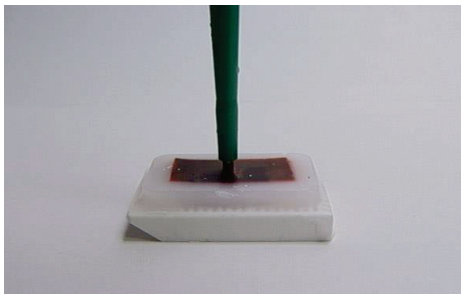
- ❑ **FFPE Specimens:**
  - ○ Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. 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:**
  - ○ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - ○ Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (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.

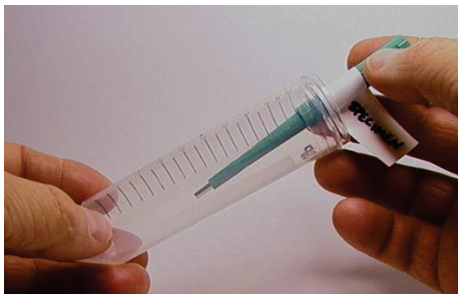
- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or phone: 415-4767864 or Fax: 415-476-5271.**

APPENDIX V (5/12/16)
NRG Oncology FFPE SPECIMEN PLUG KIT INSTRUCTIONS

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

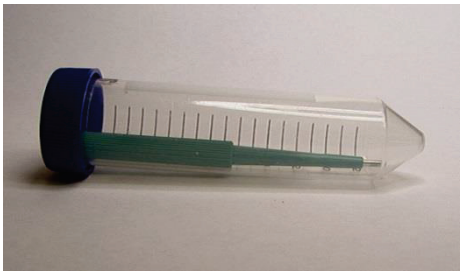


Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate 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. Include pathology accession number and block 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 NRG Oncology Biospecimen Bank 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: <u>For FFPE or Non-frozen Specimens Only</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143

Courier Address (FedEx, UPS, etc.): <u>For Frozen specimens or Trackable FFPE shipments</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
Questions: 415-476- 7864/FAX 415-476-5271; NRGBB@ucsf.edu

APPENDIX V (5/12/16)
NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS

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

Kit contents: Sites are required to provide their own blood draw tubes.

-)
- Ten (10) 1 ml cryovials
- Biohazard bags (2) and Absorbent shipping material (2)
- One Styrofoam container (inner) and Cardboard shipping (outer) box per case
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form and Kit Instructions

<u>Preparation and Processing Plasma and Whole Blood:</u>

(A) <u>Plasma</u>: <u>Purple Top EDTA tube #1 (two 5 ml or one 10 ml EDTA tube)</u>

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

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST form.
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 a minimum of 0.5 ml plasma into up to 5 cryovials as are necessary for the plasma collected labeled with NRG Oncology 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.

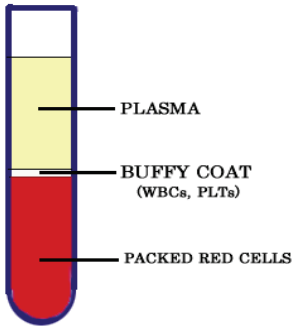
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection timepoint on ST.

(B) <u>Whole Blood For DNA: Purple Top EDTA tube #2 (one 5 ml or one 10ml EDTA tube)</u>

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

<u>Process:</u>

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 NRG Oncology 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 ST

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 NRG Oncology 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.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please Email NRGBB@ucsf.edu or call (415)476-7864

Shipping Address :
Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
415-476-7864

APPENDIX V (5/12/16)
NRG Oncology 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 NRG Oncology 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 NRG Oncology 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.
- ❑ Include all NRG Oncology 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.***
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- ❑ **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)
NRG Oncology Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115
Contact Phone: (415) 476- 7864

APPENDIX VI (2/19/14)
(NOTE: PH II-R ERLOTINIB RANDOMIZATION COMPLETED, ARM 2 CLOSED TO ACCRUAL EFFECTIVE 4/02/14)

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 VII
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 VIII: RETIRED STUDY CHAIR (11-APR-2023)

Dr. Ross Abrams retired from Rush University Medical Center after the recruitment and treatment phase of this trial. Dr. Abrams continues to serve as the Principal Investigator of this study during the post treatment phase.

Principal Investigator/Radiation Oncology
Ross A. Abrams, MD
Rush University Medical Center
Chicago IL