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

INDEX

RADIATION THERAPY ONCOLOGY GROUP

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

SCHEMA

RTOG Institution # _____

RTOG 0848 **ELIGIBILITY CHECKLIST—STEP 1 (11/17/09)**

Case # _____ (page 1 of 3)

_____ (Y) 1. Histologic proof of primar

RTOG Institution # _____

RTOG 0848 **ELIGIBILITY CHECKLIST** 9Tj /TSTEP

1.0 INTRODUCTION

The pattern of tumor relapse was recorded on the site of the first relapse only and categorized as local, regional, or distant. The distribution

RTOG 0848

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

1.6 Requirement for clear designation of tumor margin status
RTOG

3.1.14 Signed study-specific informed consent

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

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

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

3.2 Conditions for Patient Ineligibility

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

3.2.2 Patients managed with a5.1(o7.1(th)5..4(eq.491 -1.1497 TDhe)5. ri3th a)Tc-0.0018 Tw(3.2.2

4 (radiotherapy with fluoropyrimidine sensitization) as described in the schema.

- If a patient is not going on to the second randomization, step 2 of registration **must** still be completed via web registration.

5.2 General Pre-Registration Requirements

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

As a first step in the credentialing procedure, a Facility Questionnaire must be completed by all institutions entering patients on this protocol and/or an SFTP account for digital data submission must be established. The Facility Questionnai

8:30 a.m. to 5:00 p.m. ET. The registrar will ask2for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

- 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

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

A R O F W i t h i n 1 4
O N L Y :

T R

6.10.3 Organs at Risk **(3/4/10)**
Variation Acceptable

randomized to further treatment. Elevation

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

Version 2.3, March 29, 2010[1]

Alopecia

7.3.8 Supply

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

7.3.9 Accountability

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

7.3.9.1 *Accountability and Supply*

7.8 Dose Modifications (6/8/10)

Dose modifications will be made according to the greatest degree of toxicity. Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE per section 7.10).

General considerations:

Á

Toxicity on Day 15

ANC: Day 15 PLATELET: Day 15 DOSE MODIFICATION

7.8.2.2

7.8.3

7.9 Modality Review

The medical oncology co-chairs will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. Drs. Safran, Philip, and Moore will perform chemotherapy reviews. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

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

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Phase 2 and 3 Trials Utilizing an Agent unde

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

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

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

b) G3-4 myelosuppression with or without hospitalization.

7.12 CRADA

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

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA)

8.2.1 Specific Requirements

Either classic (Whipple) or pylorus-preserving pancreaticoduodenectomy should be performed. The retroperitoneal dissection along the medial

9.0 OTHER THERAPY$_e$

9.1 Permitted Supportive Therapy$_e$

All supportive therapy for optimal medical care will be given during the study period at the

the material removed at the time of surgery

patients appear particularly uncomfortable answering a question. Similarly, interviewers will give patients a short break if the patient appears otherwise in need of a few minutes break. Note: The FACIT-Fatigue has been

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) ARM 4 ONLY (6/8/10)

Item

Using the group sequential design method [Pocock, 1977] with 3 interim analyses, 640 eligible patients are required to detect an increase in MST from 17 to 22.5 months [measured from the date of second randomization (chemotherapy vs. chemotherapy followed by chemoradiation) to the date of death], translating into a hazard ratio (experimental/control) of 0.76. It is projected

will be reported. If accrual is not completed, patients will continue to be entered onto the erlotinib arm in order to answer the chemoradiation question (second randomization). For futility, the alternative hypothesis will be tested using rule C from Freidlin and Korn at a significance level of 0.005. [Freidlin, 2002] If the p-value is less than or equal to the nominal significance level boundary for rejecting the H_1 (futility), then accrual will be stopped to the

major analysis will occur after all patients have potentially been followed for 3 years, unless an early stopping rule is satisfied. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
-

(positive vs. negative) included as fixed covariat

and the effect of other known prognostic factors such as nodal status, margin status, and tumor

Gudjonsson B. Cancer of the pancreas: 50 years of surgery. Cancer 1987; 60:2284-230 603. PMID 3326 60653 60

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 combineHsu CC, radiation and chemotherapy followingsu CC, cu 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 anGorouracil after curative resection of cancer of the pancreas anG ry 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 Lgroaureos Storomipkyst(eg(PRO.1(ngMIS FIB7(s)61)35.173721(e413Tc-0.0

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)u 52–60

APPENDIX I

Informed Consent Template for Cancer Treatment Trials
(English Language)

RTOG 0848

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

(3/4/10)

(3/4/10) Study Plan Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

Randomize

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

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

Rare but serious

- Hole in the outer layer of the eye
- Inflammation (swelling and redness) of the eye)
- Hole in
- Liver fai
- Bleedin
- Severe of tissue
- Swelling
-

Dangerous int

- Low

- Bowel obstruction, which could result in abdominal pain, nausea and vomiting and may require surgery.
- Gastric, duodenal or small-bowel ulcer formation that can result in abdominal pain,

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

What are the costs of taki

It is important that you te ll your study doctor, _____

Please note: This section of the informed consent form is about additional research

We would like to keep some of the tissue that is left over for future research. The use of your tissue, blood and urine for future research is optional. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the

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

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

- **For NCI's clinical trials information, go to:**

APPENDIX II

APPENDIX V

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

Pancreas (Exocrine)

for accreditation purposes for
he Commission on Cancer. These elements may be clinically important,
ut are not yet validated or regularly used s27 (tea.s mnage)4.9le

Pancreas (Exocrine) • Digestive System CAP Approved

* Data elements ***with asterisks*** a ***not required*** e

APPENDIX VII (6/8/10)
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

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

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APPENDIX VIII (6/8/10)
RTOG URINE COLLECTION KIT/INSTRUCTIONS

This Kit contains:

- One (1) Sterile Urine collection cup
- Biohazard bags
- Absorbent Paper Towel
- Parafilm for sealing outside of cup

Urine Specimens:

Preparation for collecting **Urine:**

-

APPENDIX XI

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments: Submit**	**study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-951-CTSU		

Requirements for RTOG 0848 registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- Sites must be credentialed for either 3D-CRT or IMRT approaches
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory From must be

Commercial agents: Gemcitabine; Capecitabine

Commercial agents: Erlotinib

APPENDIX XII
EORTC GROUP-SPECIFIC INFORMATION

To come