

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG PA-0020**

**A RANDOMIZED PHASE II TRIAL OF WEEKLY GEMCITABINE, PACLITAXEL AND EXTERNAL IRRADIATION (50.4 GY) FOLLOWED BY THE FARNESYL TRANSFERASE INHIBITOR R115777 (NSC #702818) FOR LOCALLY ADVANCED PANCREATIC CANCER**

**Study Chairman**

Radiation Oncology

Tyvin Rich, M.D.  
University of Virginia  
Department of Radiation Therapy  
Health Sciences Center  
Box 383  
Charlottesville, VA 22908  
(804) 924-5191  
FAX # (804) 982-3262  
*tar4d@virginia.edu*

Medical Oncology

Howard Safran, M.D.  
(401) 793-7151  
FAX # (401) 793-5073  
*hsafran@Lifespan.org*

Surgical Oncology

John Hoffman, M.D.  
(215) 728-3518  
FAX # (215) 728-2773  
*jp\_hoffman@fcc.edu*

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## RADIATION THERAPY ONCOLOGY GROUP

### RTOG PA-0020

#### A RANDOMIZED PHASE II TRIAL OF WEEKLY GEMCITABINE, PACLITAXEL AND EXTERNAL IRRADIATION (50.4 GY) FOLLOWED BY THE FARNESYL TRANSFERASE INHIBITOR R115777 (NSC #702818) FOR LOCALLY ADVANCED PANCREATIC CANCER

#### SCHEMA

<b>S</b>	<b><u>Tumor Dimension</u></b>	<b>R</b>	<b><u>Arm 1:</u></b>
	1. < 5 cm		<u>Radiation therapy:</u> 50.4 Gy (1.8 Gy x 28 fractions)
<b>T</b>	2. ≥ 5 cm	<b>A</b>	<u>Paclitaxel:</u> 40 mg/m <sup>2</sup> /week by 1-hour i.v. infusion on days 1, 8, 15, 22, 29, 36
<b>R</b>	<b><u>Weight Loss</u></b>	<b>N</b>	<u>Gemcitabine:</u> 75 mg/m <sup>2</sup> /week on days 1, 8, 15, 22, 29, 36
	1. ≤ 10% body weight	<b>D</b>	<b><u>Arm 2:</u></b>
<b>A</b>	2. > 10% body weight		<u>Radiation therapy:</u> 50.4 Gy (1.8 Gy x 28 fractions)
<b>T</b>		<b>O</b>	<u>Paclitaxel:</u> 40 mg/m <sup>2</sup> /week by 1-hour i.v. infusion on days 1, 8, 15, 22, 29, 36
<b>I</b>		<b>M</b>	<u>Gemcitabine:</u> 75 mg/m <sup>2</sup> /week on days 1, 8, 15, 22, 29, 36
<b>F</b>		<b>I</b>	<u>R115777:</u> 300 mg p.o. b.i.d. for 21 days every 28 days, to start 3-8 weeks after the last radiation treatment and continue until disease progression or unacceptable toxicity.
<b>Y</b>		<b>Z</b>	
		<b>E</b>	<b>Two to three weeks following completion of chemoradiotherapy, all patients will be restaged by CT/MRI scan. Patients without disease progression who are randomized to Arm 2 will begin R115777 3-8 weeks after completion of chemoradiotherapy.</b>

	DAY (Arms 1 and 2)						DAY (Arm 2)
Radiation	1→5	8→12	15→19	22→26	29→33	36→38	59 (up to Day 94) start R115777 and continue until progression or unacceptable toxicity
Paclitaxel	1	8	15	22	29	36	
Gemcitabine	1	8	15	22	29	36	
R115777							

**Eligibility:** (See Section 3.0 for details)

- Pathologically confirmed, unresectable, non-metastatic adenocarcinoma of the pancreas.
- Patients with biliary or gastro-duodenal obstruction must have drainage prior to starting chemoradiation.
- All malignant disease must be encompassable within a single irradiation field (15 x 15 cm maximum).
- No malignancy (within the past two years) except for non-melanomatous skin cancer or carcinoma *in situ* of the cervix, uterus, or bladder.
- No previous chemotherapy for pancreatic cancer (Gemzar® or Taxol®).
- Radiographically assessable disease; no prior irradiation to the planned field.
- Zubrod performance status 0-1.
- Granulocytes ≥ 1,800/μl, platelets ≥ 100,000/μl, bilirubin < 2.0 mg/dL, ALT < 3x ULN, creatinine < 3.0 mg/dL.
- No significant infection or other coexistent medical condition.
- No pregnant or lactating women.
- Signed study-specific consent form prior to registration.

**Required Sample Size: 154**

RTOG Institution # \_\_\_\_\_

RTOG PA-0020

**ELIGIBILITY CHECK (10-5-01)(12/16/02)**

Case # \_\_\_\_\_

(page 1 of 2)

- \_\_\_\_\_ (Y) 1. Does the patient have a pathologically-confirmed adenocarcinoma of the pancreas?
- \_\_\_\_\_ (Y) 2. Does the patient have unresectable disease based on your institution's standardized criteria of unresectability?
- \_\_\_\_\_ (N) 3. Is there evidence of metastatic disease in the major viscera or peritoneal seeding?
- \_\_\_\_\_ (Y/N) 4. Does the patient have biliary or gastroduodenal obstruction?  
\_\_\_\_\_ (Y) If yes, does/will the patient have drainage prior to beginning chemoradiation?
- \_\_\_\_\_ (Y) 5. Is all malignant disease encompassable within a single irradiation field (15 x 15 cm maximum)?
- \_\_\_\_\_ (Y) 6. Does the patient have radiographically assessable disease?
- \_\_\_\_\_ (N) 7. Has the patient had prior radiation to the planned field?
- \_\_\_\_\_ (N) 8. Has the patient had prior paclitaxel or gemcitabine?
- \_\_\_\_\_ (Y) 9. Do the patients' laboratory values meet the criteria in Section 3.1.10?
- \_\_\_\_\_ (Y) 10. Has the required CT/MRI of the abdomen, chest X-ray, and EKG been performed within four weeks of study entry?
- \_\_\_\_\_ (N) 11. Does the patient have significant infection or other coexistent medical condition that would preclude protocol therapy?
- \_\_\_\_\_ (N) 12. Is the patient pregnant or lactating?
- \_\_\_\_\_ (N) 13. Has the patient had prior malignancies, except for non-melanomatous skin cancers, or carcinoma *in situ* of the uterus, cervix, or bladder?  
\_\_\_\_\_ (Y) If yes, has the patient been disease-free for  $\geq 2$  years?
- \_\_\_\_\_ (Y) 14. Is the patient's ZPS 0-1?

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- \_\_\_\_\_ (Y) 3. Is the patient eligible for this study?

(cont'd on next page)

RTOG Institution # \_\_\_\_\_

RTOG PA-0020

**ELIGIBILITY CHECK (10-5-01)(12/16/02)**

Case # \_\_\_\_\_

(page 2 of 2)

- \_\_\_\_\_ 4. Date the study-specific Consent Form was signed? *(must be prior to study entry)*
- \_\_\_\_\_ 5. Patient's Name
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Race
- \_\_\_\_\_ 10. Social Security Number
- \_\_\_\_\_ 11. Gender
- \_\_\_\_\_ 12. Patient's Country of Residence
- \_\_\_\_\_ 13. Zip Code
- \_\_\_\_\_ 14. Patient's Insurance Status
- \_\_\_\_\_ 15. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ (N) 16. Is the patient going to receive IMRT?
- \_\_\_\_\_ 17. Is the weight loss  $\leq 10\%$  or  $> 10\%$ ?
- \_\_\_\_\_ 18. Is the maximum tumor dimension  $< 5$  cm or  $\geq 5$  cm?
- \_\_\_\_\_ 19. Medical Oncologist's Name
- \_\_\_\_\_ 20. Treatment Start Date
- \_\_\_\_\_ 21. Treatment Assignment

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

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background and Preliminary Data**

There are approximately 29,000 new cases of pancreatic carcinoma each year in the United States. The overall 5-year survival has remained constant at < 5%.<sup>1</sup> Approximately half of all patients have locally advanced, unresectable disease at the time of initial diagnosis. Standard treatment for locally advanced disease is fluorouracil (5-FU) and external beam irradiation.<sup>2</sup> The addition of 5-FU as radiosensitizing agent modestly increases local control and median survival; however, virtually all patients will eventually develop disease progression and death.<sup>2,3</sup> More effective treatments are clearly needed.

### **1.2 Paclitaxel/RT**

The RTOG is evaluating novel radiosensitizers to attempt to improve local disease control for locally advanced pancreatic cancer. Paclitaxel synchronizes cells at G2/M, a relatively radiosensitive phase of the cell cycle.<sup>4-6</sup> In addition, response to paclitaxel and concurrent radiation (*paclitaxel/RT*) is not affected by p53 mutations suggesting that paclitaxel/RT is a rationale treatment approach for malignancies which frequently harbor p53 mutations such as pancreatic cancer.<sup>7</sup>

The Brown University Oncology Group has completed phase I and II studies of paclitaxel/RT for patients with locally advanced pancreatic cancer.<sup>8</sup> The maximum tolerated dose (MTD) of paclitaxel was 50 mg/m<sup>2</sup>/week for 6 weeks with 50 Gy abdominal radiation. The dose limiting toxicities were abdominal pain within the radiation field, nausea and anorexia. Forty patients were then treated on a phase II study. The overall response rate was 29% with a 1-year survival of 37%. The incidence of grade 3-4 GI toxicity was less than 10%. Based on this data, the RTOG has completed a confirmatory phase II trial (*RTOG 98-12*) of paclitaxel/RT in 122 patients with locally advanced pancreatic cancer. Preliminary analysis suggests a one year survival of 50% and a median survival of 12 months. This one year survival is approximately an 85% relative improvement over the previous RTOG study 92-09 of 5-FU and concurrent radiation for locally advanced pancreatic cancer. Grade 3-4 toxicity was infrequent suggesting that other radiation sensitizers could be added to improve local control. Novel agents are needed to prevent or delay the development of systemic metastases.

### **1.3 Gemcitabine**

Gemcitabine is one of the most active single agents for pancreatic cancer. The initial phase II study by Casper et al. evaluated gemcitabine in 44 patients with advanced pancreatic cancer at doses of 800-1,250 mg/m<sup>2</sup>/week, and reported a partial response rate of 11% and a 23% one year survival.<sup>9</sup> In a phase II study by Carmichael et al. of 32 patients, an objective response rate of 6.3% was obtained.<sup>10</sup> In both of these studies, patients appeared to have improvement of symptoms even without objective tumor response. A multi-center randomized trial by Burris compared gemcitabine to 5-FU.<sup>11</sup> Clinical benefit, response, and survival were evaluated. Clinical benefit was defined by monitoring three variables: pain, Karnofsky Performance Status, and weight. Gemcitabine treated patients experienced a 23.8% clinical benefit compared to 4.8% of the 5-FU treated patients ( $P=0.0022$ ). The median survival was 5.65 versus 4.41 months ( $P=0.0025$ ) for the gemcitabine and 5-FU arm, respectively, and the 1 year survival was 18% versus 2%. All patients progressed within 14 months of starting therapy, and none survived beyond 19 months. An objective tumor response rate of 5.4% for gemcitabine and 0% for 5-FU was reported. Tempero et al. has demonstrated that a slower gemcitabine infusion rate of 10 mg/m<sup>2</sup>/min rather than the standard 30 minute infusion may achieve a higher response rate and prolonged survival.<sup>12</sup>

### **1.4 Gemcitabine/RT**

*In vitro* investigations suggest that gemcitabine is a potent radiation sensitizer.<sup>13</sup> Phase I studies of gemcitabine/RT have been performed in pancreatic cancer. Hoffman et al. administered gemcitabine at dose levels of 300-600 mg/m<sup>2</sup>/week x 6 weeks with 50 Gy.<sup>14</sup> Toxicities included gastritis, enteritis and neutropenia. Kudrimoti et al. evaluated a 24 hour continuous infusion of gemcitabine with concurrent radiation for patients with unresectable GI malignancies.<sup>15</sup> Patients received gemcitabine, 50-150 mg/m<sup>2</sup>/week, with 40 Gy +/- boost. The MTD of gemcitabine was 125 mg/m<sup>2</sup>/week; the dose limiting toxicities were nausea and diarrhea.

Blackstock et al. evaluated a twice-weekly gemcitabine dosing schedule utilizing gemcitabine dosages of 20-60 mg/m<sup>2</sup>/week.<sup>16</sup> The most common toxicity was hematologic. Of the six patients followed for > 6 months, one complete and one partial response were observed. Based on these data, the CALGB initiated and completed a phase II study of gemcitabine, 40 mg/m<sup>2</sup>, twice weekly, with concurrent radiation for

locally advanced pancreatic cancer. These studies clearly establish the potential of gemcitabine to produce radiosensitization.

### **1.5 Gemcitabine + Paclitaxel**

The combination of gemcitabine and paclitaxel is demonstrating promising activity with acceptable toxicity in NSCLC, bladder cancer, and breast cancer.<sup>17-20</sup>

Gemcitabine and paclitaxel are each radiation sensitizers in locally advanced pancreatic cancer. The Brown University Oncology Group has completed a phase I study combining paclitaxel, gemcitabine and radiation. Patients with locally advanced pancreatic cancer received 50.4 Gy radiation, paclitaxel, 40 mg/m<sup>2</sup>/week and escalating doses of gemcitabine. The initial dose level of gemcitabine, 75 mg/m<sup>2</sup>/week for 6 weeks, was the MTD. Gemcitabine dose levels of 150 mg/m<sup>2</sup> and 110 mg/m<sup>2</sup> were also evaluated. Eight patients were treated at the gemcitabine 75 mg/m<sup>2</sup> dose level. Of these eight patients, only one had grade 3 toxicity consisting of anorexia and dehydration. Four patients responded and three had stable disease; this included one patient who underwent resection after chemoradiation and had a pathologic complete response and a second patient with a near complete pathologic response. Three patients were treated at the gemcitabine dose level of 150 mg/m<sup>2</sup>/week; grade 3 GI toxicity including diarrhea, nausea and anorexia developed in all three patients and one patient also had grade 3 myelosuppression. An intermediate dose level of gemcitabine, 110 mg/m<sup>2</sup>, was subsequently added. Three of four patients had grade 3 or 4 toxicities. One these patients had a grade 4 hypersensitivity pneumonitis that responded to prednisone. Based on this phase I study, the dose level of gemcitabine 75 mg/m<sup>2</sup>/week, paclitaxel 40 mg/m<sup>2</sup>/week and 50.4 Gy concurrent radiation will be investigated in this phase II study. This dose level was well tolerated with major activity including a pathologic complete response. This novel combination of radiation sensitizers may have substantially more activity than either agent alone with acceptable toxicity.

More active chemoradiation may improve loco-regional control and more effectively palliate symptoms. However, at the low doses used for radiosensitization, it is unlikely that conventional chemotherapy agents have substantial systemic activity to prevent the growth of micrometastases. This protocol will evaluate the farnesyl protein transferase (*FPTase*) inhibitor R115777 after paclitaxel/gemcitabine/radiation.

### **1.6 Farnesyl Protein Transferase (*FPTase*) Inhibitors**

FPTase inhibitors were developed following two and one half decades of investigations of the *ras* oncogenes and the proteins they encode. The *ras* genes [Harvey (*Ha*), Kristen (*Ki*), and N-*ras*] encode low molecular weight proteins, called Ras.<sup>21</sup> Ras, after several post-translational modifications, localizes itself to the inner surface of the plasma membrane.<sup>22</sup> In normal cells, Ras proteins cycle between GDP-bound (*inactive*) and GTP-bound (*active*) forms to regulate cellular proliferation and differentiation. When certain growth factors bind to their cellular receptors, this causes activation of the GDP- bound Ras protein which exchanges its bound GDP for GTP. This activated form of the Ras protein subsequently triggers a cascade of events that ultimately lead to cell proliferation. The GTPase activity of ras then turns off the biological event, Ras returns to its inactive form (*GDP-bound*), and the cycle is thus closed. Ras then remains in an inactive form until a new growth signal arrives.<sup>23</sup>

A single point mutation changing an amino acid is responsible for altering the wild-type *ras* gene into an oncogene that efficiently induces neoplastic transformation.<sup>21</sup> The mutations in *ras* genes which are frequently found in cancer inhibit the GTPase activity of the Ras protein, thus Ras remains bound to GTP and permanently activated. This results in the active Ras protein constitutively stimulating cell growth and proliferation.<sup>24</sup>

Mutations of the *ras* gene are found in 90% of pancreatic tumors.<sup>25</sup> Thus, inhibition of *ras* gene function is a rational target in pancreatic cancer. Recent progress at blocking ras-induced cell transforming activity has centered on inhibiting the enzyme farnesyl-protein transferase.<sup>26</sup> Membrane localization of Ras is essential for its normal function and the cell transforming activity of its mutated, oncogenic form. Membrane anchoring of Ras is achieved through a series of post-translational modifications. The first and most critical modification is farnesylation of its carboxyl-terminal motif, catalyzed by farnesyl protein transferase (*FPTase*).<sup>21</sup> Inhibition of the farnesylation reaction by synthetic FPTase inhibitors nullifies ras membrane anchorage and therefore inhibits Ras protein function as well as its cell transforming capability.<sup>24-26</sup> Recent evidence suggests that inhibition of farnesylation of other proteins may contribute to the antitumor effect of farnesyl transferase inhibitors.

## **1.7 R115777**

R115777 is a potent and selective nonpeptidomimetic inhibitor of farnesyl protein transferase (*FPTase*) both *in vitro* and *in vivo*. It has been shown in several preclinical tests to inhibit H-ras, K-ras and N-ras activity in transformed tumors.

R115777 inhibits the human *FPTase* farnesylation of a laminin B peptide substrate with an  $IC_{50}$  of 0.86 nM. R115777 also inhibited the farnesylation of a peptide substrate harboring the mutated K-ras B sequence with an  $IC_{50}$  of 7.9 nM.<sup>27</sup> Isoprenylation catalyzed by a different enzyme, geranylgeranyltransferase type I (*GGTase I*), was only 40% inhibited at 50 $\mu$ M of R115777, therefore, demonstrating specificity of R115777 for *FPTase*.

In intact tumor cells in culture, R115777 produced antiproliferative effects at nanomolar concentrations. These antiproliferative effects are seen at the same nanomolar concentrations as those that inhibit the enzyme. Two human colon cancer cell lines, LoVo and HCT116, transformed by an activated K-rasB oncogene, were growth-inhibited by R115777 with  $IC_{50}$ 's of 16 and 22 nM respectively. The same cell lines that had not been transformed by K-rasB were growth-inhibited by much higher concentrations of R115777. The human pancreatic cell line CAPAN-2, which harbors a mutant K-ras gene, was growth-inhibited with an  $IC_{50}$  of 16 nM.

In nude mice bearing subcutaneous CAPAN-2 tumors, R115777 administered orally (*b.i.d.*) significantly inhibited tumor growth at doses of 50 and 100 mg/kg. A 56% reduction of final tumor weight was observed at the 50 mg/kg dose level, and a 76% reduction of final tumor volume was observed at the 100 mg/kg dose level.

The first phase I trial, R115777-USA-1, was conducted at the National Cancer Institute. A 5-day q12 hour dosing regimen was utilized with inpatient and outpatient dose-escalation scheme. Doses of R115777 were escalated in 3 cycles with a rest period of 7-9 days between cycles. The starting dose for the first cohort was 25 mg q 12 hrs. A total of 27 patients received 84 cycles of therapy. Protocol defined maximum tolerated dose (*MTD*) was not achieved at the highest dose level (1300 mg *b.i.d.* for five days). One dose limiting toxicity (*DLT*) was encountered in the 1300 mg *b.i.d.* cohort. This patient with a prior history of paclitaxel-induced peripheral neuropathy developed burning of the oral area, vagina and lower extremities (*Grade 3*) on Day 4 of the first cycle. The symptoms subsided after the cessation of R115777 only to return in a milder form (*Grade 1*) during the second cycle (*dose reduced to 800 mg b.i.d.*). One patient at the 1300 mg dose level had a transient increase in creatinine from 1.1 to 3.3 mg/dL. Two of 7 subjects at 800 mg and 4 of 6 patients in the 1300 mg *b.i.d.* cohort experienced *Grade 2* fatigue. Hematologic toxicity was mild, as two patients developed one day of *Grade 3* neutropenia.

Plasma concentrations of R115777 were determined by a validated HPLC-method. Peak concentrations of drug were reached within 2 hours after intake for the oral solution and within 4 hours for the beaded capsule. Results suggested a dose-linear relationship in  $C_{max}$  and  $AUC_{0-12h}$ . The terminal half-life ranged between 5 and 28 hours. The twice-daily dosing regimen was supported by the pharmacokinetic profile. A statistical covariate analysis revealed that the steady-state oral clearance of R115777 was not influenced by the demographic factors of age, gender, body weight, body surface area (*BSA*) and race.

A 21 day chronic dosing regimen using the capsule formulation has been investigated at the Fox Chase Cancer Center and in Europe. *DLT*s of myelosuppression and fatigue were observed at dose levels > 600 mg p.o. *b.i.d.* Hematologic *DLT* related to R115777 was observed in 25% of patients at doses of 500 – 550 mg *b.i.d.* Of the 11 patients treated at 400 mg *b.i.d.* in the chronic dosing phase I trials, myelosuppressive *DLT* was seen in 2 patients during the first two weeks of treatment. Only 1 of 8 patients have developed myelosuppressive *DLT* at 300 mg *b.i.d.*, and one patient developed *Grade 3* diarrhea after dose escalating from 200 mg.

In this RTOG phase II trial for patients with locally advanced disease, patients on Arm 2 will receive R115777 until disease progression. Since patients will require long term administration, a relatively nontoxic schedule is preferred. A dosage of 300 mg p.o. *b.i.d.* for 21 days every 28 days has therefore been selected.

### **Special Toxicity Report Summary (11/22/02)**

A review of the toxicities/ adverse events (AE) associated with chemoradiation was undertaken per the protocol guidelines by the Study Chairs, GI Committee Chair, the RTOG Statistical Center, and RTOG Headquarters. Evaluation of the first 15 patients was done. When it was found that 10 of 15 patients experienced at least one Grade 3 adverse event, with varying relationships to protocol treatment, a conference call was held on September 19, 2002. The decision was made that Grade 3 or higher gastrointestinal or pulmonary toxicities were the important toxicities to be monitored. It was agreed that a more detailed analysis of the toxicities should be performed on the first 30 patients entered onto the study as soon as possible. At the time of the second conference call ( *October 4, 2002*), the available results were as follows:

- 28 of the first 30 patients have toxicity data available;
- 17 of 28 (61%) experienced at least one Grade 3 toxicity;
- 8 of 28 (29%) experienced Grade 3 gastrointestinal toxicity;
- no Grade 3 or higher pulmonary toxicities were reported;
- no Grade 4 or grade 5 toxicities were reported.

The Study Chairs and the GI Committee considered the toxicity profile to be acceptable thus far. The decision was made to continue the study treatment as designed, and to continue study accrual. The toxicity/AE data will continue to undergo very close monitoring.

## **2.0 OBJECTIVES**

- 2.1** To determine the one-year survival rates of patients treated with paclitaxel, gemcitabine, and radiation with or without R115777.
- 2.2** To determine the toxicity and loco-regional activity of paclitaxel, gemcitabine and radiation.
- 2.3** To determine the feasibility and toxicity of prolonged administration of R115777 after paclitaxel, gemcitabine and radiation.
- 2.4** To evaluate whether R115777 can increase progression-free and overall survival after chemoradiation for locally advanced pancreatic cancer.

## **3.0 PATIENT SELECTION**

### **3.1 Eligibility Criteria**

- 3.1.1** Pathologically confirmed adenocarcinoma of the pancreas.
- 3.1.2** Patients must have unresectable disease based on institutional standardized criteria of unresectability. There must be no evidence of metastatic disease in the major viscera and no peritoneal seeding or ascites.
  - 3.1.2.1** Patients with residual disease after resection (*R-1 or -2, micro and macroscopic residual*) are eligible.
- 3.1.3** Patients with biliary or gastroduodenal obstruction must have drainage prior to starting chemoradiation.
- 3.1.4** All malignant disease must be encompassable within a single irradiation field (*15 x 15 cm maximum*). If equivalent square fields are larger than 15 x 15 cm (*AP/PA*), the radiation oncologist study chair must be contacted for discussion.
- 3.1.5** All patients must have radiographically assessable disease.
- 3.1.6** EKG, chest x-ray, abdominal CT/MRI scan must be obtained within four weeks of study entry.
- 3.1.7** No previous irradiation to the planned field; no previous chemotherapy for pancreatic cancer (*Gemzar® or Taxol®*).
- 3.1.8** No malignancy (*within the past two years*) except non-melanomatous skin cancer or carcinoma in situ of the cervix, uterus, or bladder.
- 3.1.9** Zubrod performance status 0-1.
- 3.1.10** Required entry laboratory parameters: granulocytes  $\geq 1,800/\mu\text{l}$ , platelet count  $\geq 100,000/\mu\text{l}$ , bilirubin  $< 2.0 \text{ mg/dL}$ , ALT  $< 3 \times$  upper limit of normal, creatinine  $< 3.0 \text{ mg/dL}$ .
- 3.1.11** Patients must not have significant infection or other coexistent medical condition that would preclude protocol therapy.
- 3.1.12** No pregnant or lactating women. It is unknown what effects R115777 may have on the developing fetus.
- 3.1.13** Signed study-specific consent form prior to study entry.

## **4.0 PRETREATMENT EVALUATIONS**

### **4.1 Mandatory for Study Entry**

**4.1.1** History and physical, CBC, differential, platelets, BUN, creatinine, Na, K, AST, ALT, total bilirubin, liver function tests, glucose, total protein, albumin, and pregnancy test should be performed within 14 days of study entry. Repeat laboratories should be obtained within 48 hours of study entry for abnormal laboratory values or if there is clinical evidence of patient deterioration. EKG, chest x-ray, abdominal CT/MRI scan must be obtained within 4 weeks of study entry. (*See Section 11.1*)

## **5.0 REGISTRATION PROCEDURES**

**5.1** Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Demographic Data
- Treatment Start Date

## **6.0 RADIATION THERAPY**

### **6.1 Total Dose**

**6.1.1** 50.4 Gy, 28 fractions, 5.5 weeks (*1.8 Gy/day*). A cone down after 45 Gy will be performed to encompass gross or microscopic disease with a margin of 1-1.5 cm.

**6.1.2** The prescription point will be designated at the intersection of the multiple beams.

**6.1.3** There are no planned interruptions.

### **6.2 Volume**

**6.2.1** Simulation of the gross tumor volume (*GTV*) will be determined with intravenous bolus contrast administration given during CT or MRI.

**6.2.2** Primary or planning CT target volume (*PTV<sub>1</sub>*) will include the *GTV* (*with 2 to 3 cm margins in all directions*), areas of proven nodal involvement (*with 2 to 3 cm margins*), and the draining lymph nodes.

**6.2.3** The boost planning target volume (*PTV<sub>2</sub>*) will include the *GTV* (*with 1 to 1.5 cm margin on all sides*) including proven nodal involvement.

**6.2.4** Treatment must be individualized based on the volume and location of disease.

**6.2.5** The PTV must be digitized or drawn on the planning CT scan DRRs or on standard orthogonal X-ray films.

**6.2.6** All fields treated will be simulated. The initial volume irradiated will include the tumor as defined on CT and MRI scans, as well as areas of potential or proven nodal involvement with a 2 to 3 cm margin in all directions for the initial 45 Gy.

### **6.3 Equipment**

**6.3.1** Linear acceleration with photon beams of 10 MV or higher energy. In some situations, small patients may be treated with a lower energy beam after approval by Dr. Rich.

### **6.4 Field Borders for the Initial PTV**

The initial volume should include the level of T10-11 superiorly to cover the celiac axis nodes. The inferior field border is typically placed at the level of L3 or lower in order to encompass the entire tumor. This will generally be 4-5 cm to the right of the midline. The left lateral margin should extend 2 to 3 cm beyond the tumor. The lateral fields should include the portal vein, the hepatic artery, and the common bile duct as well as the head of the pancreas with the appropriate margin.

### **6.5 Technique**

The uniformity requirement will be +/- 5% of the total dose at the prescription point within the planning target volume. The preferred technique for radiation will be a three or four field technique using anterior, posterior, left and right lateral field with the patient in a supine position. Other techniques, including multifield 3D conformal therapy, may be used to cover the PTV, provided that the normal tissue constraints below (*Section 6.6 and 6.7*) are appropriately met.

### **6.6 Kidney Dose**

The dose to the kidney will require careful monitoring and kidney volumes must be defined on simulation fields. The equivalent of one kidney should receive  $\leq 20$  Gy or at least the equivalent of 2/3 of one kidney

must be spared from the radiotherapy fields. If only a single functioning kidney is present at least 2/3 of the functioning kidney must be excluded from any radiation port. For head lesions,  $\geq 50\%$  of the right kidney is often in the AP/PA field (s) and so  $\geq 2/3$  of the left kidney should be shielded. For body or tail lesions,  $\geq 50\%$  of the left kidney is often with the AP/PA field(s) and so  $\geq 2/3$  of the right kidney should be shielded.

#### **6.7 Spinal Cord and Liver Dose**

The spinal cord dose shall be limited to 45 Gy. No more than one-half of the volume of the liver should be contained within the radiation field ( $>30$  Gy). If severe toxicity develops during external beam radiation therapy, the course of treatment may require interruption or modification as specified in the protocol. An isodose distribution of the treatment on a transverse plane containing the central axis indicating the position of the kidneys, the spinal cord, and the liver is required.

#### **6.8 Quality Assurance Documentation**

**6.8.1** Within seven days after the start of treatment, the following data should be forwarded to RTOG Headquarters (*ATT: Dosimetry*).

**6.8.1.1** CT Scan and/or MRI showing the extent of the tumor with contrast; Radiographs or DRRs designating the GTV (*including lymph nodes considered to contain tumor*), liver, spinal cord, and kidneys, for AP and lateral fields; the RT prescription; the RT calculations and portal films corresponding to the simulation films or DRR's, a copy of the daily calculations and any relevant beam data associated with any modifications of treatment submission.

**6.8.1.2** A copy of the daily treatment record, isodose distribution on a transverse plane containing the central axis indicating the positions of the spinal cord, liver and kidneys, DVHs if the treatment planning system provides this output, and boost films (*simulation and portal*) must be submitted to RTOG Headquarters within 1 week of RT end.

**6.8.1.3** Questions concerning the radiotherapy technique should be addressed to Dr. Rich (804-243-6517), or email: [tar4d@virginia.edu](mailto:tar4d@virginia.edu).

### **7.0 DRUG THERAPY:**

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

#### **7.1 Paclitaxel (Taxol®)**

**7.1.1** *Formulation:* Paclitaxel is a poorly soluble plant product from the western yew, *Taxus brevifolia*. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf-life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

**7.1.2** *Preparation:* A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (*Cremophor EL*) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel will be diluted to a final concentration of 0.3 to 1.2 mg/ml in D<sub>5</sub>W, USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (*DEHP*) plasticizer from polyvinyl chloride (*PVC*) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (*NOTE: acceptable limits established by the USP Particular Matter Test for LVP's*) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (*e.g.: Millex-GV Millipore Products*) into the i.v. fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used. **(8-16-02)**

**7.1.3** *Administration:* Paclitaxel, at the appropriate dose and dilution, will be given as a 1-hour infusion. The paclitaxel is mixed in D<sub>5</sub>W in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI% with 0.22 m in-line filter. Paclitaxel will be administered via an infusion control device (*pump*) using non-PVC tubing and connectors, such as the i.v. administration sets (*polyethylene or polyolefin*) which are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered. **(8-16-02)**

**7.1.4** *Storage:* Paclitaxel vials should be stored between 2°-25°C (36°-77°F).

**7.1.5** *Adverse Effects:*

- Hematologic: Myelosuppression

- Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (*AST, ALT, bilirubin, alkaline phosphatase*) hepatic failure, hepatic necrosis.
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (*MI*), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness.
- Neurological: Sensory (*taste*), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma.
- Allergy: Anaphylactoid and urticarial reactions (*acute*), flushing, rash, pruritus.
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (*erythema, induration, tenderness, rarely ulceration*), and radiation recall reaction.

**7.1.6** *Supplier:* Commercially available.

**7.2** **Schedule of Paclitaxel**

**7.2.1** Paclitaxel dosage will be 40 mg/m<sup>2</sup>/week for six weeks. Paclitaxel will be delivered in the outpatient setting as an intravenous infusion over 1 hour on days 1, 8, 15, 22, 29 and 36.

**7.2.2** Premedicate with dexamethasone 10-20 mg i.v. 30 minutes prior to paclitaxel, diphenhydramine, 25 mg i.v., 30 minutes prior to paclitaxel; ranitidine (*or other H2 blocker*), 50 mg i.v., 30 minutes prior to paclitaxel.

**7.2.3** Patients will be attended by medical personnel for the first 15 minutes of infusion and then have blood pressure checked every 15 minutes for one hour, then as needed. Medications for acute management of anaphylaxis should be readily available in the location where the patient is being treated.

**7.3** **Gemcitabine HCl (Gemzar®)**

**7.3.1** Formulation

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

**7.3.2** Preparation

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

**7.3.3** Administration

An appropriate amount of drug will be prepared with normal saline and administered as a 30 minute infusion or at a rate not faster than 10mg/m<sup>2</sup>/min.

**7.3.4** Storage and Stability

The lyophilized product should be stored at controlled room temperature (*20° to 25° C*) (*68° - 79° F*). Once the drug has been reconstituted it should be stored at controlled room temperature and used within 24 hours.

**7.3.5** Adverse Effects

The major side effects observed with gemcitabine include leukopenia, thrombocytopenia, anemia, and a collection of signs and symptoms referred to collectively as a flu-like syndrome with fever, headache, rigors, myalgia, and anorexia. Less common side effects include abnormal liver function tests, kidney damage, proteinuria, hematuria, chills, nausea, vomiting, diarrhea, constipation, itchy skin rash, malaise, anorexia, cough, runny nose, insomnia, sweating, hypotension, drowsiness, peripheral edema, dyspnea, difficulty in breathing and stomatitis.

**7.3.6** Dosage of Gemcitabine

Gemcitabine dosage will be 75 mg/m<sup>2</sup>/week for six weeks. Gemcitabine will be delivered in the outpatient setting as an intravenous infusion over 30 minutes on days 1, 8, 15, 22, 29, and 36.

**7.4** **Toxicity and Dose Modification of Gemcitabine and Paclitaxel**

Non-hematologic Toxicity: Paclitaxel, gemcitabine and radiation will be held for any Grade 3 or Grade 4 nonhematologic toxicity. Treatment will not be resumed until non-hematological toxicity has resolved to no greater than Grade 2. When treatment is resumed, patients will receive a 50% dose reduction of gemcitabine and paclitaxel; dose reductions are permanent. If a second episode of Grade 3 or Grade 4 nonhematologic toxicity occurs, patients may complete radiation but will not receive additional gemcitabine or paclitaxel.

Hematologic Toxicity: The dose of gemcitabine, paclitaxel, and radiation will be modified according to blood counts on the day of treatment. Blood counts will be evaluated weekly.

Treatment Day Blood Counts		Dosage
ANC	Platelet Count	
> 1,000/ $\mu$ l	> 75,000/ $\mu$ l	Full dosage gemcitabine and paclitaxel
500-999/ $\mu$ l	50,000 – 75,000 $\mu$ l	No gemcitabine or paclitaxel; resume at 50%
< 500/ $\mu$ l	< 50,000 $\mu$ l	Hold XRT and chemotherapy; resume at 50%.

Patients who have required two dose reductions and experience a third episode of ANC < 1,000/ $\mu$ l or platelets < 75,000/ $\mu$ l may complete radiation but will not receive additional gemcitabine or paclitaxel.

Patients who experience a severe hypersensitivity reaction to paclitaxel may be rechallenged with paclitaxel following additional premedication with dexamethasone at the discretion of the treating physician. Patients developing hypersensitivity pneumonitis should not receive additional gemcitabine or paclitaxel.

## **7.5 R115777**

### **7.5.1 Formulation**

R115777 is being supplied through the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis, National Cancer Institute. R115777 will be supplied in 100 mg tablets.

R115777 may be requested from the NCI by completing a Clinical Drug Request (*NIH- 986*) and mailing it to the Drug Management and Authorization Section, Pharmaceutical Management Branch, NCI, EPN Room 7149, Bethesda, MD 20892, or faxing it to (301) 480- 4612. The Clinical Drug Request Form (*NIH-986*) can be found under “Forms” on the CTEP homepage (<http://ctep.info.nih.gov>). For questions, call (301) 496- 5725.

### **7.5.2 Storage and Stability**

R115777 will be stored at room temperature, 15-25° C. Shelf life stability studies are ongoing. **(8-16-02)**

### **7.5.3 Administration**

At initial study registration, patients will be randomized to chemoradiation alone or chemoradiation followed by R115777. Two to three weeks following the last radiation treatment, all patients will be restaged by CT/MRI scan. Patients with disease progression will be removed from protocol therapy, but will continue to be followed. All patients randomized to R115777, without disease progression after chemoradiation, will begin R115777 within 3-8 weeks following last radiation treatment. All toxicities from chemoradiation must have resolved to grade 1 or less.

The dose of R115777 will be 300 mg p.o. b.i.d. for 21 days every 28 days, and will not be modified for surface area or body weight. The drug should be given with a meal. Drug doses must be separated by intervals of 10 hours. Patients will continue on R115777 until disease progression or unacceptable toxicity. Neurologic assessment should be performed and documented prior to beginning R115777 therapy because of the potential for this type of toxicity. **(8-16-02)**

### **7.5.4 Adverse Effects of R115777(6/16/04)**

The major side effects with R115777 may include leukopenia, thrombocytopenia, neutropenia, anemia, abnormal liver function tests, increase in lipase, kidney damage, kidney failure, proteinuria, nausea, vomiting, diarrhea, constipation, pruritus, skin rash/desquamation, malaise, anorexia, asthenia, lethargy, ataxia, weakness, peripheral, motor, and sensory neuropathy photosensitivity, hemoglobinemia, platelet changes, confusion, mood changes, infection, and thrombosis/thrombus/embolism.

There may be an interaction between Coumadin® and R115777, so patients who are on Coumadin® therapy may require more frequent monitoring of their anticoagulation by their physicians. **(8-16-02)**

### **7.5.5 R115777: Dose Modifications**

R115777 will be temporarily held for any grade 3 or grade 4 hematologic or nonhematologic toxicity, or grade 2 peripheral neuropathy (*objective sensory loss or paresthesia interfering with function but not with activities of daily living*).

R115777 therapy can be reinstated at the time of toxicity resolution to  $\leq$  Grade 1. The dose will then be reduced to 200 mg b.i.d for 21 days every 28 days. Should a subject encounter unacceptable toxicity after the first dose reduction, a second dose reduction to 100 mg b.i.d. for 21 days every 28 days will be permitted once the drug related toxicity has diminished to Grade 1 or resolved. Two dose reductions will be the maximum permitted. Subjects developing a third episode of grade 3 or grade 4 toxicity will be

taken off of treatment. Subjects undergoing dose reductions will not be permitted to re-escalate at a later time. If a toxicity does not resolve by day 42, the patient should be removed from protocol treatment.

**7.6 Concomitant Medications (8-16-02)**

Patients may receive all concomitant therapy deemed necessary to provide adequate support, with the exception of the therapies detailed below:

- No other investigational agents may be used during the study.
- No other cytotoxic agents or radiotherapy may be used during the study.
- Antacids may be used up to two hours before R115777.

**7.7 Adverse Event Reporting**

**7.7.1** The revised NCI Common Toxicity Criteria (CTC) Version 2.0 (3/98) will be used to score chemotherapy and acute radiation ( $\leq 90$  days) toxicities and can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). This study will be monitored by the Clinical Data Update System (CDUS) Version 1.1. Complete cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol, which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days, and telephoned to RTOG HQ within 24 hours of discovery.

**7.7.1.1** Any ADR which is both serious (*life threatening, fatal*) and unexpected (*phone report within 24 hours; written report within 10 days*).

**7.7.1.2** Any increased incidence of a known ADR which has been reported in the package insert or the literature.

**7.7.1.3** Any death on study if clearly related to the commercial agent(s).

**7.7.1.4** Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. The AML/MDS form should be completed in place of the FDA 3500 form.

**7.7.2** The ADR report **during chemoradiation** should be documented on Form FDA 3500 and mailed to:

**RTOG Headquarters**  
**1101 Market Street**  
**Philadelphia, PA 19107**  
**(215) 574-3214**  
**FAX (215) 928-0153**

**Investigational Drug Branch**  
**P.O. Box 30012**  
**Bethesda, MD 20824**  
**(301) 230-2330 (available 24 hours)**  
**FAX (301) 230-0159**

**7.7.3** Expedited Reporting for Phase II and Phase III Studies (including hospitalization defined in bullet 1 below [for patients receiving R115777 only]):

UNEXPECTED EVENTS		EXPECTED EVENTS	
Grades 2 – 3 Attribution Possible, Probable, or Definite	Grades 4 and 5 Regardless of Attribution	Grades 1 - 3	Grades 4 and 5 Regardless of Attribution
Expedited report within 10 working days.  (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB and RTOG within 24 hours. Expedited report to follow within 10 working days.  This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.  Any late death attributed to the agent ( <i>possible, probable, or definite</i> ) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited report to IDB and RTOG, including <b>Grade 5</b> Aplasia in leukemia patients, within 10 working days.  This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution.  Any late death attributed to the agent ( <i>possible, probable, or definite</i> ) should be reported within 10 working days.  <b>Grade 4</b> Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.

- For **hospitalization** only – Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (*or prolongation of existing hospitalization*) must be reported regardless of expected or unexpected and attribution.
- Telephone reports to the Investigational Drug Branch at (301) 230-2330 available 24 hours daily (*recorder between 5pm and 9 am EST*).

Expedited reports are to be submitted using ADeERS or the paper templates available at <http://ctep.info.nih.gov>. The NCI Guidelines for expedited adverse event reporting are also available at this site. For sites without internet access, please call Data Management at RTOG HQ.

- A list of agent-specific expected adverse events can be found in the protocol.
- For this study, serious adverse events occurring during XRT, prior to initiation of R115777, do not require expedited reporting, but must be reported via CDUS quarterly.

**7.8** Clinical Trials Agreement

The agent(s) (*hereinafter referred to as “Agent[s]”*), used in this protocol is/are provided to the NCI under a Clinical Trials Agreement (CTA) with Janssen Pharmaceutica. Therefore, the following obligations/guidelines apply to the use of the Agent(s) in this study:

Agent(s) may not be used 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 should be maintained as such by the investigators.

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

- a) NCI must provide all Collaborators with 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 which 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 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.
- d) The NCI encourages investigators to make data from clinical trials fully available to Collaborator(s) for review at the appropriate time (*see e*). Clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.
- e) 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.
- f) Any data provided to Collaborator(s) 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.
- g) Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

**Regulatory Affairs Branch, CTEP, DCTD, NCI**  
**Executive Plaza North, Room 718**  
**Bethesda, Maryland 20892**  
**FAX (301) 402-1584**

The Regulatory Affairs Branch will then distribute them to Collaborator(s).

## **8.0 SURGERY**

In patients with a marked response to treatment, surgery may be attempted based on the discretion of the attending surgeon.

## **9.0 OTHER THERAPY**

Not applicable to this study.

## **10.0 PATHOLOGY**

### **10.1 RTOG Tissue Bank**

**10.1.1** Patients entered on this study must submit materials to the RTOG Tissue Bank.

**10.1.2** The following must be provided:

**10.1.2.1** One H&E stained slide.

**10.1.2.2** A paraffin-embedded tissue block of the tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

**10.1.2.3** Pathology report documenting that submitted block or slides contain tumor.

**10.1.2.4** A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

**10.1.3** RTOG will reimburse pathologists from submitting institutions \$100. per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).

**10.1.4** Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).

10.1.5 Materials will be sent to:

Amy Furness  
LDS Hospital  
Dept. of Pathology  
E.M. Laboratory  
8<sup>th</sup> Ave & C Street  
Salt Lake City, UT 84143  
(801) 408-5626  
FAX (801) 408-5020  
Ldafurne@ihc.com

**11.0 PATIENT EVALUATION**

**11.1 Assessments (8-16-02)**

	Within 2 weeks prior to study entry	Weekly Chemorad	Chemorad Completion	During R115777	Arm 1 Post-chemoradiation; Arm 2 Post-R115777
History	X				
Performance Status	X		X	q28 days	Follow-up
Physical Examination: <sup>d</sup>	X	X	X	q28 days	Follow-up
Vital Signs	X	X	X	q28 days	Follow-up
Neurologic Assessment			X <sup>f</sup>	q28 days	X <sup>g</sup>
Toxicity Notation		X	X	Weekly	Follow-up
CBC, Diff, Plt <sup>e</sup>	X <sup>a</sup>	X <sup>c</sup>	X	Weekly	X <sup>g</sup>
Glucose, Lytes, BUN, Creatinine, LDH, AST, ALT, Total Bili, LFT's, TP, Alb <sup>e</sup>	X <sup>a</sup>		X	q14 days	X <sup>g</sup>
Pregnancy test <sup>h</sup>	X				
EKG	X <sup>b</sup>			X <sup>g</sup>	X <sup>g</sup>
Chest x-ray	X <sup>b</sup>		X	X <sup>g</sup>	X <sup>g</sup>
Abdominal CT/MRI <sup>d</sup>	X <sup>b</sup>		X	q 3 mos.	q 3 mos.

- a. Repeat laboratories should be obtained within 48 hours of study entry for abnormal laboratory values or if there is clinical evidence of patient deterioration.
- b. Radiologic studies and EKG must be done within 4 weeks of study entry.
- c. Once weekly during chemoradiation.
- d. Patients randomized to no further therapy after chemoradiation are required to have a physical exam every 3 months, and abdominal CT/MRI every 3 months.
- e. Blood tests should be done within 3 weeks of start of R115777.
- f. For patients randomized to Arm 2.
- g. As clinically indicated.
- h. To be performed in all females with childbearing potential.

## **11.2 Response Assessment**

### **11.2.1 Measurement of Response**

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

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

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

#### **11.2.1.1 Guidelines for Evaluation of Measurable Disease**

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

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

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

### **11.2.2 Response Criteria**

Response and progression will be measured by comparing tumor size at time of study entry with measurements taken at completion of chemoradiation and every 3 months thereafter. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination.

#### **11.2.2.1 Evaluation of target lesions-RECIST criteria**

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

## **12.0 DATA COLLECTION**

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX# 215/928-0153)

### **12.1 Summary of Data Submission (4/28/04)**

<b>Item</b>	<b>Due</b>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Pathology Slides/Blocks (P2)	
Preliminary Dosimetry Information: RT Prescription ( <i>Protocol Treatment Form</i> ) (T2) Films ( <i>simulation and portal</i> ) (T3)/or DRR's Calculations (T4) Treatment Planning CT/MRI Scan (C1)	Within 1 wk of start of RT
Treatment Summary Form (TF)	Within 1 week after chemo day 15; within 1 week after chemo day 36
Final Dosimetry Information: Radiotherapy Form (T1) Daily Treatment Record (T5) Iosodose Distribution (T6) Boost Films ( <i>simulation and portal</i> ) (T8)	Within 1 week of RT end
Initial Followup Form (FS)	90 days from start of RT
Follow-up Form (F1)	Every 3 months from FS for 2 years; every 6 months to year 5; then annually. Also at progression/relapse and at death.
Treatment Flowsheet (F8)	Within 1 week of completion of each 28 day cycle.
Surgery Form (S1)	As applicable
Autopsy Report (D3)	As applicable

### **12.2 Site Records**

Site records must contain details regarding dosage, and start and stop dates of study drug R115777 treatment. These records include documentation of tracking treatment compliance; i.e., medical record notes, notations of telephone calls to the patient, patient diaries, etc.

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints**

**13.1.1** To estimate the one-year overall survival rate for each regimen (*failure: death due to any cause*).

**13.1.2** To determine the frequency of patients developing unacceptable toxicity (*defined as Grade 3 or highergastrointestinal or pulmonary toxicity and/or discontinuation of treatment*) attributable to protocol treatment for each regimen. (11/22/02)

**13.1.3** To estimate the one-year survival difference between the two treatment regimens.

**13.1.4** To estimate the one-year progression-free survival rate for each regimen (*failure: local, regional or distant progression, or death due to any cause*).

### **13.2 Sample Size**

The primary objective of this study is to estimate the one-year overall survival rate for each regimen. In the previous RTOG protocol for unresectable pancreatic cancer (*RTOG 98-12*), a one-year survival rate of approximately 50% was observed. Using the method of Dixon and Simon,<sup>28</sup> a sample size of 69 analyzable patients per arm followed over 12 months will ensure at least 80% probability of detecting a minimum of 15% improvement in the one-year survival rate compared to RTOG 98-12 at the 0.05 significance level (*with a one-sided test*). Adjusting this figure by 10% to allow for patient ineligibility or loss, **a total sample size of 154 patients will be required** for this study.

A secondary endpoint of this study is to estimate the difference in 1-year survival for the two treatment arms. If we assume a binomial distribution, then this difference can be estimated with a 95% confidence interval with a margin of error  $\leq 17.2\%$ .

### **13.3 Patient Accrual**

RTOG 98-12 accrued 122 patients in 16 months, for an average accrual of 7.6 patients per month. Based upon this accrual rate, accrual should be completed in approximately 20 months. If the average monthly accrual is less than 2 cases per month, the study will be re-evaluated with respect to feasibility.

### **13.4 Randomization Scheme**

Patients will be randomized to one of two treatment schedules in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.<sup>29</sup> Based upon analyses of past RTOG and institutional pancreas studies, patients will be stratified by weight loss in preceding 6 months ( $> 10\%$  vs.  $\leq 10\%$ ) and tumor dimension ( $\geq 5\text{ cm}$  vs.  $< 5\text{ cm}$ ).

### **13.5 Suspension of Accrual Due to Excessive Toxicity**

#### **13.5.1 Unacceptable Rate of Toxicity**

The rate of unacceptable toxicity from chemoradiation (*prior to treatment with R115777*) will be evaluated after the first 15 patients have been treated on either arm. Since all patients will be treated with the same regimen of gemcitabine, paclitaxel, and radiation, we can combine the arms for purposes of toxicity evaluation. The study chairs have determined that a rate of 50% will be deemed unacceptable. With 5 or less in the first 15 patients, we have  $> 91\%$  confidence that the true rate of unacceptable toxicity is  $< 50\%$ . If there are 6 or more unacceptable toxicities, we have  $< 79\%$  confidence that the true rate is  $< 50\%$ . Therefore, if there are 6 or more unacceptable toxicities in the first 15 patients, accrual will be suspended, and all data pertaining to the events will be reviewed by the study chairs and reported to the RTOG Research Strategy Committee for review. The results of this review will determine whether or not to lower the chemotherapy dose.

#### **13.5.1.1 Special Toxicity Report Summary (11/22/02)**

A review of the toxicities/ adverse events (AE) associated with chemoradiation was undertaken per the protocol guidelines by the Study Chairs, GI Committee Chair, the RTOG Statistical Center, and RTOG Headquarters. Evaluation of the first 15 patients was done. When it was found that 10 of 15 patients experienced at least one Grade 3 adverse event, with varying relationships to protocol treatment, a conference call was held on September 19, 2002. The decision was made that Grade 3 or higher gastrointestinal or pulmonary toxicities were the important toxicities to be monitored. It was agreed that a more detailed analysis of the toxicities should be performed on the first 30 patients entered onto the study as soon as possible. At the time of the second conference call (*October 4, 2002*), the available results were as follows:

- 28 of the first 30 patients have toxicity data available;
- 17 of 28 (61%) experienced at least one Grade 3 toxicity;
- 8 of 28 (29%) experienced Grade 3 gastrointestinal toxicity;
- no Grade 3 or higher pulmonary toxicities were reported;
- no Grade 4 or grade 5 toxicities were reported.

The Study Chairs and the GI Committee considered the toxicity profile to be acceptable thus far. The decision was made to continue the study treatment as designed, and to continue study accrual. The toxicity/AE data will continue to undergo very close monitoring.

#### **13.5.2 Fatal Treatment Morbidity**

If there is any fatal treatment morbidity, the event will be reported to the study chairs for review.

### **13.6 Analysis Plan**

#### **13.6.1 Interim Reports**

Interim reports will be prepared every six months until the final analysis. In general, these reports include the patient accrual rate with projected completion date; institutional accrual; pretreatment characteristics of patients accrued; the quality of submitted data with respect to timeliness, completeness, and accuracy; compliance rates of treatment delivery with respect to the protocol prescription; the frequency and severity of toxicities due to chemotherapy and radiation therapy.

#### **13.6.2 Analysis for Reporting the Initial Treatment Results**

The major analysis for reporting the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are: tabulation of all cases entered, and any patients excluded from the analysis with reasons for exclusion;

institutional accrual; distribution of important prognostic baseline variables; patient accrual rate; observed results with respect to the endpoints described in Section 13.1.

The estimated survival for each treatment will be tested against the RTOG 98-12 trial with a one-sided test.

Estimates of the median and one-year progression-free and overall survival rates and the difference in one-year survival of the two treatments will be calculated along with their associated 95% confidence intervals.

Further subgroup analyses will not be undertaken because of the small sample sizes involved in each subgroup.

**13.6.3** *Inclusion of Women and Minorities*

In conformance with the National Institutes of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have considered differences in prognosis by race and gender. In an analysis of the RTOG pancreas database, we found no difference. No other study so far has indicated any significant racial or gender differences in treatment effects for unresectable pancreatic cancer patients. These issues are not well studied. The study was designed to test the efficacy under the assumption of the same efficacy across the genders and across the races. A statistical analysis will be performed to examine the possible difference between the genders and among the races. The following table gives the projected number of patients in each race and gender group, based on the results of the previous unresectable pancreas study, RTOG 98-12.

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other or Unknown	Total
Female	0	2	7	2	0	75	0	86
Male	0	0	11	2	0	55	0	68
Total	0	2	18	4	0	130	0	154

## REFERENCES

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics 1998. *CA* 48:6-29, 1998
2. Rich T, Radiation therapy for pancreatic cancer. In *Pancreas cancer*. Howard Reber, ed. Houma Press, 1998
3. Rich TA, Evans DB. Preoperative combined modality therapy for pancreatic cancer. *World J Surg* 19:264-269, 1995.
4. Geard CR, Jones JM, Schiff, PB. Taxol and radiation. *J Natl Cancer Inst* 1993;15:89-94, 1993.
5. Tishler R, Schiff P, Geard C, Hall E. Taxol: a novel radiation sensitizer. *Int J Radiat Oncol Biol Phys* 1992;22:613-617.
6. Choy H., Rodriguez F.F., Koester S., Hilsenbeck S., et al, 1993. Investigation of Taxol as a potential radiation sensitizer. *Cancer*, 71:11, 3774-3778.
7. Safran H, King T, Choy H, Gollerkeri A, Kwakwa H, Lopez F, Myers J, Tarpey J, Moulton A, Rosmarin A. p53 mutations do not predict response to paclitaxel/radiation for non-small cell lung cancer. *Cancer* 78:1209-1216, 1996
8. Safran H, King T, Choy H, Hesketh P, Wolf B, Altenhein E, Sikov W, Rosmarin A, Akerley W, Radie-Kayne K, Cicchetti G, Lopez F, Bland K, Wanebo H. Paclitaxel and Concurrent Radiation for Locally Advanced Pancreatic and Gastric Cancer: A Phase I Study. *J Clin Oncol* 15:901-907,1997
9. Casper, E. S. Green M. R. Kelsen, D. P. Heelan, R. T. Brown, T. D. Flombaum, C. D. Trochanowski, B. Tarassoff, P. G.: Phase II trial of gemcitabine (2', 2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs* 12, 29-34 (1994)
10. Carmichael, J. Fink, U. Russell R. C. G. Spittle, M. F. Harris, A. Spiessi, G. Blatter, J.: Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer* 73, 101-5 (1995)
11. Burriss, H. A. Moore, M. J. Anderson, J. Green, M.R. Rothenberg, M. L. Modiano, M. R. Cripps, C. C. Portenoy, R. K. Storniolo, A. M. Tarassoff, P. Nelson, R. Dorr, F. A. Stephens, C. D. von Hoff, D. D.: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer- a randomized trial. *J Clin Oncol* 15, 2403-2413 (1977)
12. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J. randomized phase II trial of dose intense gemcitabine by standard infusion vs. fixed dose rate in metastatic pancreatic adenocarcinomas. *Proc Am Soc Clin Oncol* 18 273a, 1999 (abstr 1048)
13. Lawrence T: Gemcitabine as a radiation sensitizer: *Semin Oncol* 22:68-71, 1995.
14. Hoffman JP, McGinn CJ, Szarka C, et al: A phase I study of preoperative gemcitabine (GEM) with radiation therapy (RT) followed by postoperative GEM for patients with localized, resectable pancreatic adenocarcinoma (PAC). *Proc Am Soc Clin Oncol* 18:283a, 1998. (abstr 1090)
15. Kudrimot M, Regine W, John W, et al: Concurrent infusional gemcitabine and radiation in the treatment of advanced unresectable GI malignancy: A phase I/II Study. *Proc Am Soc Clin Oncol* 18:242a 1999 (abstr 929).
16. Blackstock AW, Bernard SA, Richards F, et al: Phase I study twice-weekly gemcitabine and concurrent radiation in patients with advanced pancreatic cancer. *J Clin Oncol* 17:2208-2212, 1999
17. Glisson SD, Fleming D, Michelson G, et al. A phase I study of gemcitabine and paclitaxel in patients with solid malignancies. *Proc Am Soc Clin Oncol* 18: 212a, 1999 (abstr 814)
18. Lim N, Lara PN, Edelman MJ, et al. Phase I trial of gemcitabine (GEM) plus paclitaxel (Tax) in advanced solid tumors: Preliminary results of a novel 21 day schedule. *Proc Am Soc Clin Oncol* 18: 218a 1999, (abstr 839)
19. Martin C, Isla D, Gonzale-Larriba JL, et al: A phase II study of bi-weekly gemcitabine/paclitaxel in advanced non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 18:462a, 1999 (abstr 1871)

20. Fontaine CC, Neyns BB, Grauwels DD, et al: A phase I/II study of paclitaxel and gemcitabine in patients with advanced non small cell lung cancer (NSCLC) Proc Am Soc Clin Oncol 18: 503a, 1999 (abstr 1941).
21. D.R. Lowy, & B.M. Willumsen: Function and regulation of Ras. *Annu Rev Biochem* 62, 851-91 (1993).
22. AD Cox, & CJ Deer: The ras/cholesterol connection: implications for ras oncogenicity. *Crit Rev Oncog* 3, 365-400 (1992)
23. N. E. Kohl, F.R. Wilson, S.C. Mosser, E. Giuliani, S.J. DeSolms, M.W. Conner, N. J. Anthony, W.J. Holtz, R. P. Gomez, T. Lee, R. L. Smith, S.L. Graham, G. D. Hartman, J. B. Gibbs, & A. Oliff: Protein farnesyltransferase inhibitors block the growth of ras-dependent tumors in nude mice. *Proc Natl Acad Sci* 91, 9141-9145 (1994)
24. N.E. Kohl, M.W. Conner, J. B. Gibbs, S. L. Graham, G.D. Hartman, & A. Oliff: Development of inhibitors of protein farnesylation as potential chemotherapeutic agents. *J Cell Biochem (supp)* 22, 145-150 (1995)
25. H. Reuveni, A. Gitler, E. Poradosu, C. Gilon, & A. Levitzki: Synthesis and biological activity of semipeptoid farnesyltransferase inhibition. *Bioorg and Med Chem* 5, 85-92 (1997)
26. J. Gibbs, & A. Oliff: The potential of farnesyltransferase inhibitors as cancer chemotherapeutics. *Annu Rev Pharmacol Toxicol* 37, 143-66 (1997)
27. Zhang F, Kirschmeier P, Carr D, et al. Characterization of Ha-Ras, N-Ras, Ki-Ras4A, and Ki-Ras4B as in Vitro Substrates for Farnesyl Protein Transferase and Geranylgeranyl Protein Transferase Type 1. *The Journal of Biological Chemistry*, April 1997, vol. 272, no. 15, pp. 10232-10239.
28. Dixon DO, Simon R. Sample Size Considerations for Studies Comparing Curves Using Historical Controls. *Journal of Clinical Epidemiology* 41: 1209-1213, 1988.
29. Zelen M. The randomization and stratification of patients to clinical trials. *Journal of Chronic Disease* 27:365-375, 1994.

## **APPENDIX I**

**RTOG PA-0020**

### **SAMPLE CONSENT FOR RESEARCH STUDY**

#### **A RANDOMIZED PHASE II TRIAL OF WEEKLY GEMCITABINE, PACLITAXEL AND EXTERNAL IRRADIATION (50.4 GY) FOLLOWED BY THE FARNESYL TRANSFERASE INHIBITOR R115777 (NSC #702818) FOR LOCALLY ADVANCED PANCREATIC CANCER**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know", is available from your doctor.

You are being asked to take part in this study because you have pancreatic cancer.

#### **WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to find out what effects, good and bad, the chemotherapy drugs paclitaxel (*Taxol*®) and gemcitabine (*Gemzar*®) have in combination with radiation treatment on your type of cancer. Another purpose of this study is to determine whether R115777, an experimental oral medication, can help to delay your cancer from growing back after chemotherapy and radiation.

This study is being done to determine if paclitaxel, gemcitabine, radiation and R115777 can improve the treatment of patients with pancreatic cancer. Currently, there is no cure for this type of cancer.

#### **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 154 people will take part in this study.

#### **WHAT IS INVOLVED IN THE STUDY? (8-16-02)**

If you agree to participate in this study, you will be randomized by computer (like a coin flip) to determine if you will receive either Treatment #1: paclitaxel, gemcitabine and radiation, or Treatment #2: paclitaxel, gemcitabine and radiation

followed by R115777. The chance you will receive the R115777 is about fifty-fifty.

- All patients will receive:

**Radiation Therapy:** Radiation treatment to the abdomen will be given once a day, 5 days a week, for 5 and a half weeks. All radiation treatments will be given as an outpatient at your institution.

**Chemotherapy:** Starting the same day as your radiation treatments, you will receive paclitaxel and gemcitabine once a week for 6 weeks. Paclitaxel and gemcitabine will be injected into a vein (intravenously) and will last for about one and a half hours. Your chemotherapy treatments will be given as an outpatient at your institution.

About 2 to 3 weeks after you have finished treatment with paclitaxel, gemcitabine and radiation, you will have a CT/MRI scan of your abdomen to see whether your pancreatic cancer has changed in size. If your cancer is the same size or smaller, you will begin taking R115777 or have no further therapy. R115777 is an experimental oral medication. You will take three pills twice daily for 21 days every 28 days; therefore, you will not take R115777 for seven days. Then you will start again and take it for 21 days on and seven days off. R115777 will begin at least three weeks after your last radiation treatment and after all the side effects from the paclitaxel, gemcitabine and radiation have gone away. The medication should be taken with a meal; the two daily doses must be separated by a time span of 10 hours. The R115777 will be provided to you free-of-charge by the National Cancer Institute.

If you take part in this study, you will have the following tests and procedures:

Procedure

Physical Exam

Schedule

Prior to study entry, weekly during chemotherapy and radiation treatment, at the end of the chemotherapy and radiation treatment, and then according to the follow-up schedule. If patient is to receive R115777, the physical exam will be done every month during R115777 administration.

Neurologic Assessment

If patient is to receive R115777, at the end of the chemotherapy and radiation treatment, and then monthly during R115777 administration.

Blood Counts	Prior to study entry, once weekly during chemotherapy and radiation treatment, at the end of the chemotherapy and radiation treatment. If patient is to receive R115777, blood counts will be done within three weeks of starting drug, and then weekly during R115777 administration.
Blood Chemistries	Prior to study entry, at the completion of chemotherapy and radiation treatment. If patient is to receive R115777, blood chemistries will be done within three weeks of starting drug, and then every 2 weeks during R115777 administration.
Pregnancy Test	Prior to study entry.
Abdominal CT/MRI Scan	Prior to study entry, at the end of the chemotherapy and radiation treatment, then every three months after completion of chemotherapy and radiation for the rest of your life.
Chest X-Ray	Prior to study entry, at the end of the chemotherapy and radiation treatment, then as clinically indicated.
EKG	Prior to study entry; as clinically indicated

- Follow-up visits with your physician will be scheduled every three months for two years, every 6 months to year 5, and then annually.

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central office for review and research investigation associated with this protocol.

The tests may include research into biologic factors and inherited traits (*genes*) that may help to predict and treat pancreatic cancer in the future.

Your tissue may be helpful for research, but probably will not help you. It might help people who have cancer and other diseases in the future. Reports/findings about the research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

You may call 801-408-5626 at a later time if you change your mind about allowing the use of your stored tissue for additional tests.

### **HOW LONG WILL I BE IN THE STUDY?**

You will receive radiation therapy for five and a half weeks. During that time, chemotherapy will be given once a week. About three weeks after your last radiation treatment and when all the side effects from the gemcitabine, paclitaxel and radiation have resolved, you will receive either R115777 or no further therapy. R115777 is an oral medication taken twice a day for 21 days every 28 days. You will continue taking the R115777 indefinitely unless your disease gets worse or you have side effects from the medication. Follow-up visits will continue for the rest of your life according to the above schedule.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

### **WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiation, chemotherapy, and R115777 are stopped, but in some cases side effects can be serious or long-lasting or permanent.

#### **Risks Associated with Gemcitabine, Paclitaxel and Radiation Therapy**

##### *Very Likely*

Nausea and vomiting

Stomach pain and gastrointestinal discomfort, which usually occurs during the last three weeks of chemotherapy and radiation and generally goes away within 2-4 weeks after the treatment is finished.

Diarrhea

Fatigue

Tanning, redness of skin and hair loss within the treatment area which is temporary

Skin in treatment area may remain permanently dry

Lower blood counts

Loss of appetite and weight loss  
Loss of hair

Less Likely

Fever, muscle aches, rash  
Constipation  
Headaches  
Tingling in your hands or feet, muscle weakness, confusion  
Skin or nail darkening  
Sores in the mouth  
Skin rash or peeling of skin on hands and feet

Less Likely, But Serious

Chest pain or irregular heartbeat; decrease in blood pressure  
Allergic reactions  
Stevens-Johnson Syndrome (rash)  
Change in liver function  
Decrease in kidney function.  
Shortness of breath, cough, inflammation or scarring of the lung. If you develop difficulty with breathing or cough, you should contact your doctor immediately.

**Risks Associated with R115777 (8-16-02) (6/16/04)**

Very Likely

Lower blood counts that can lead to a risk of infection and bleeding  
Nausea and/or vomiting  
Diarrhea or constipation  
Loss of appetite and weight loss  
Fatigue  
Infection  
Blood clots

Less Likely

Tingling or numbness in your hands or feet, muscle weakness, confusion, mood changes  
Skin rash or skin irritation/peeling  
Light sensitivity  
Change in pancreatic function

Less Likely, But Serious

Possible cataract (clouding of the lens in the eye) or decreased color vision  
Kidney damage or swelling; kidney failure  
Change in liver function that can lead to a risk of infection and hospitalization

If you are a patient receiving Coumadin® therapy (to decrease the clotting ability of your blood), there may be an interaction between Coumadin® and R115777. Patients on Coumadin® may require more frequent blood tests to monitor the clotting ability of their blood.

**Reproductive Risks:** Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

### **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with pancreatic cancer in the future.

### **WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; or (3) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Please talk to your regular doctor about these and other options.

### **WHAT ABOUT CONFIDENTIALITY?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives from Janssen Pharmaceutica, and other groups or organizations that have a role in this study.

**WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

The Division of Cancer Treatment, and Diagnosis, NCI, will provide you with the investigational agent free of charge for this study. Every effort has been made to ensure adequate supplies of the investigational agent(s), free of charge, for all participants. If, however, the investigational agent(s) become(s) commercially available while you are being treated, there is a possibility that you would be asked to purchase subsequent supplies.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A group of experts in pancreatic cancer from the RTOG Gastrointestinal\_Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study. (11/22/02)

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

*(This section must be completed)*

For information about your disease and research-related injury, you may contact:

\_\_\_\_\_
Name

\_\_\_\_\_
Telephone Number

For information about this study, you may contact:

\_\_\_\_\_  
Name

\_\_\_\_\_  
Telephone Number

For information about your rights as a research subject, you may contact:

*(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)*

\_\_\_\_\_  
Name

\_\_\_\_\_  
Telephone Number

### **WHERE CAN I GET MORE INFORMATION?**

You may call the NCI's Cancer Information Service at  
**1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615**

Visit the NCI's Web sites for comprehensive clinical trials information  
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ  
<http://cancernet.nci.nih.gov>.

### **SIGNATURE**

**I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.**

**I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).**

\_\_\_\_\_  
Patient Signature (*or legal Representative*)

\_\_\_\_\_  
Date

### **TISSUE AND BLOOD TESTING (RTOG PA-0020)**

I agree to the use of my tissues/other samples for research studies related to my cancer.

Yes     No

\_\_\_\_\_  
Patient Signature (*or legal Representative*)

\_\_\_\_\_  
Date

## APPENDIX II

### **KARNOFSKY PERFORMANCE SCALE**

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

### **ZUBROD PERFORMANCE SCALE**

0	Fully active, able to carry on all predisease activities without restriction ( <i>Karnofsky 90-100</i> ).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work ( <i>Karnofsky 70-80</i> ).
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 ( <i>Karnofsky 50-60</i> ).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours ( <i>Karnofsky 30-40</i> ).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair ( <i>Karnofsky 10-20</i> ).

### APPENDIX III

#### **STAGING FOR PANCREAS** *AJCC, 5<sup>th</sup> Edition*

##### **Primary Tumor (T)**

- TX Primary tumor cannot be assessed  
T0 No evidence of primary tumor  
Tis *in situ* carcinoma  
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 directly into any of the following: duodenum, bile duct, peripancreatic tissues or direct invasion of the ampulla of Vater  
T4 Tumor extends directly into any of the following: stomach, spleen, colon, adjacent large vessels

##### **Regional Lymph Nodes (N)**

- NX Regional lymph nodes cannot be assessed  
N0 No regional lymph node metastasis  
N1 Regional lymph node metastasis  
    pN1a Metastasis in a single regional lymph node  
    pN1b Metastasis in multiple regional lymph nodes

##### **Distant Metastasis (M)**

- MX Presence of distant metastasis cannot be assessed  
M0 No distant metastasis  
M1 Distant metastasis, or seeding of the peritoneum, or direct extension to an organ or structure not listed in T1-3

##### **Stage Grouping**

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

## APPENDIX V

### ADVERSE EVENT REPORTING GUIDELINES

#### A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
  - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (*as outlined above*) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (*in the case of RTOG-coordinated intergroup studies*) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

#### B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (*grade 4*) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

### **C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS**

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

#### **Commercial and Non-Investigational Agents**

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions ( $\geq$  *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities ( $\geq$  *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

#### **Investigational Agents**

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)  
P. O. Box 30012  
Bethesda, MD 20824  
Telephone number available 24 hours  
(301) 230-2330 FAX # 301-230-0159

#### **i. Phase I Studies Utilizing Investigational Agents**

- All deaths during therapy with the agent.

Report **by phone** within 24 hours to IDB and RTOG Headquarters.

\*\*A written report to follow within 10 working days.

- All deaths within 30 days of termination of the agent. As above

- All life threatening (*grade 4*) events which may be due to agent. As above

- First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.  
\*\*A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours  
\*\*A written report must be sent to RTOG within 10 working days with a copy to IDB. (*Grade 4 myelosuppression not reported to IDB*)

- All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.  
\*\*A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. \*\*Report **in writing** to RTOG Headquarters and IDB within 10 working days.

\*\* See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form