

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG C-0128

### A PHASE I/II STUDY OF COX-2 INHIBITOR, CELEBREX™ (*CELECOXIB*), AND CHEMORADIATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER

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#### SCHEMA

##### Treatment

**R** Pelvic RT:  
45 Gy given in 25 once-daily fractions (1.8 Gy/fraction) Monday-Friday over 5 weeks

**E** ↓  
LDR\* x 2 or HDR x 5

**G** ↓  
Parametrial boost (if indicated)

**I**

**S** Celebrex™:  
Start on Day 1 of RT, daily for 12 months (400 mg p.o. b.i.d., total 800 mg daily ; AM dose 3 hours prior to RT)

**T**

**E** 5-FU:  
Patients will receive 5-FU by continuous infusion on days 2-5, days 23-26, days 44-47.  
(1000 mg/m<sup>2</sup> daily x 4 days, three cycles)

**R** Cisplatin\*\*  
Patients will receive cisplatin (75 mg/m<sup>2</sup>, maximum dose 150 mg) as a 1-2 hour infusion on days 1, 22, and 43

\* If LDR brachytherapy is utilized, the third cycle of chemotherapy should be delivered at the time of the implant.

\*\*Cisplatin should be administered within 16 hours of the first radiation fraction. 5-FU may start within one hour after the completion of cisplatin, but no more than 36 hours after completion of cisplatin.

##### **Eligibility:** (See Section 3.0 for details) (8/20/02)

- Advanced squamous, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix FIGO stage IIB-IVA or patients with FIGO stage IB-IIA with biopsy-proven pelvic node metastases and/or tumor size  $\geq 5$  cm.
- No disease outside of the pelvis.
- Zubrod Performance Status 0-2.
- WBC  $\geq 3,000/\text{mm}^3$ ; AGC  $\geq 1,500/\text{mm}^3$ ; platelets  $\geq 100,000/\text{mm}^3$ ; total bilirubin  $\leq 1.5$  mg/dl; serum creatinine  $\leq 1.5$  mg/dl; AST or ALT  $\leq 2.5$  x ULN; serum calcium  $\leq 1.3$  x ULN; creatinine clearance  $\geq 50$  cc/min.
- No patients with active GI ulcers, GI bleeding, or inflammatory bowel disease.
- No history of allergy to sulfonamides or NSAIDs or Celebrex™ use two months prior to study entry.
- No patients that are taking dilantin or lithium; no active cardiac disease.
- No prior malignancies unless disease-free  $> 3$  years or concurrent malignancies (except basal cell carcinoma).
- No patients that are known HIV positive.
- No prior surgery for cervical cancer, pelvic irradiation, chemotherapy, or para-aortic disease.
- No pregnant or lactating females.
- Signed study-specific informed consent prior to study entry.

**Required Sample Size: 83**

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

RTOG C-0128

**ELIGIBILITY CHECK** (8/1/01, 8/20/02)

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

(page 1 of 3)

- \_\_\_\_\_(Y) 1. Does the patient have histologically confirmed squamous, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix?
- \_\_\_\_\_(Y) 2. Does the patient have FIGO stage IIB to IVA or FIGO stage IB to IIA with biopsy-proven pelvic node metastases and/or tumor size  $\geq 5$  cm?
- \_\_\_\_\_(N) 3. Is there disease outside of the pelvis?
- \_\_\_\_\_(0-2) 4. What is the patient's Zubrod score?
- \_\_\_\_\_(Y) 5. Confirm the following labs within two weeks of study entry:
- \_\_\_\_\_(Y) WBC  $\geq 3,000/\text{mm}^3$
- \_\_\_\_\_(Y) Absolute granulocyte count  $\geq 1,500/\text{mm}^3$
- \_\_\_\_\_(Y) Platelets  $\geq 100,000/\text{mm}^3$
- \_\_\_\_\_(Y) Total bilirubin  $\leq 1.5$  gm/dl
- \_\_\_\_\_(Y) Serum creatinine  $\leq 1.5$  mg/dl
- \_\_\_\_\_(Y) AST or ALT  $\leq 2.5$  x institutional upper normal limit
- \_\_\_\_\_(Y) Serum calcium  $\leq 1.3$  x institutional upper normal limit
- \_\_\_\_\_(Y) Creatinine clearance  $\geq 50$  cc/minute (*see Section 3.1.4*)
- \_\_\_\_\_(N) 6. Does the patient have a history of allergy or hypersensitivity to sulfonamides, NSAIDS, or Celebrex<sup>TM</sup>?
- \_\_\_\_\_(N) 7. Is the patient known to be infected with HIV?
- \_\_\_\_\_(N) 8. Has the patient had prior surgery for carcinoma of the cervix other than biopsy?
- \_\_\_\_\_(N) 9. Does the patient have para-aortic disease?
- \_\_\_\_\_(N) 10. Except for transvaginal irradiation for bleeding, has the patient had previous pelvic radiation therapy or systemic chemotherapy?
- \_\_\_\_\_(N) 11. Is the patient pregnant or lactating?
- \_\_\_\_\_(Y/N) 12. Is there a history of previous cancer or simultaneous malignancies (*other than cutaneous basal cell carcinoma*)?
- \_\_\_\_\_(Y) If yes, has the patient been disease free for  $> 3$  years?
- \_\_\_\_\_(N) 13. Has the patient taken Celebrex<sup>TM</sup> or any other COX-2 inhibitor within the last two months?

(cont'd on next page)

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

RTOG C-0128

**ELIGIBILITY CHECK** (8/1/01, 8/20/02)

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

(page 2 of 3)

- \_\_\_\_\_(N) 14. Is the patient taking dilantin or lithium?
- \_\_\_\_\_(N) 15. Based on the physician's review, is the patient taking any medications which would interfere with the metabolism of Celebrex<sup>TM</sup>?
- \_\_\_\_\_(N) 16. Does the patient have active cardiac disease?
- \_\_\_\_\_(N) 17. Does the patient have a medical condition that would limit survival to less than six months?
- \_\_\_\_\_(N) 18. Does the patient have a psychiatric illness that would prevent informed consent?
- \_\_\_\_\_(N) 19. Does the patient have a medical condition that would prevent the use of full-dose chemotherapy?
- \_\_\_\_\_(N) 20. Does the patient have active GI ulcers, GI bleeding, or inflammatory bowel disease?

**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?
- \_\_\_\_\_ 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

(cont'd on next page)

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

**RTOG C-0128**

**ELIGIBILITY CHECK (8/1/01, 8/20/02)**

**Case #**

*(page 3 of 3)*

- \_\_\_\_\_ 14. Patient's Insurance Status
- \_\_\_\_\_ 15. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ 16. Treatment Start Date
- \_\_\_\_\_ (Y/N) 17. Is this patient going to receive IMRT?
- \_\_\_\_\_ 18. Medical Oncologist's Name
- \_\_\_\_\_ 19. 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**

Chemoradiotherapy has been shown in RTOG 90-01 and several GOG studies to be more effective than radiation therapy alone in the treatment of women with advanced carcinoma of the cervix.<sup>1-6</sup> The combination of cisplatin and 5-fluorouracil decreased both local and distant recurrence rates and improved overall survival in RTOG 90-01.<sup>1</sup> GOG 120 demonstrated superior survival for weekly cisplatin and radiotherapy compared with radiotherapy alone, and weekly cisplatin and radiotherapy yielded a lower frequency of combined grade 3 and grade 4 toxicity compared with the combination of radiotherapy, cisplatin, 5-FU, and hydroxyurea.<sup>2</sup> In the arm that received radiotherapy and cisplatin, the rate of progression-free survival was 67%, and thus, within two years 33% of the patients with advanced cervical cancer had failed therapy. The combination of Celebrex™ and cisplatin-based chemotherapy with radiotherapy has the potential to improve tumor control and reduce complications in women with advanced carcinoma of the cervix. Preliminary evidence suggests that inhibition of COX-2 can down-regulate angiogenesis and work cooperatively with radiation therapy without enhancing the normal tissue toxicity. A phase I/II study to assess the feasibility and toxicity of this regimen is proposed.

### **1.2 Cervical Cancer**

**1.2.1** It is estimated that in the United States, in 2001, 12,900 new cases of invasive cervical carcinoma will be diagnosed; of these cases, 4,400 women will die from the disease. For early-stage disease, IB/IIA, radiation therapy or definitive surgery yields five-year survival of 85-90%. For women with more advanced lesions, the five-year survival rates decline significantly.

**1.2.2** The NCI Consensus Conference previously determined that for patients with bulky tumors or advanced stage disease, radiation therapy to the pelvis is the preferred therapy. However, at that time there was no recommendation regarding the benefit of concomitant chemotherapy and radiation therapy for women with advanced disease. With the recent results of RTOG 90-01 and four other cooperative group trials, the NCI has issued a Clinical Alert which recommends that advanced cervical cancer be treated with chemoradiation.

### **1.3 Concurrent Chemoradiotherapy and COX-2 Inhibition**

**1.3.1** A strategy to improve survival of patients with malignant disease has been the addition of chemotherapy to definitive radiation therapy. In cancers of the head and neck, bladder, rectum, anus, esophagus and lung, concurrent chemoradiotherapy has been shown to improve local control, disease-free survival, distant disease-free survival and/or overall survival. RTOG 90-01, a prospective randomized phase III study of locally advanced carcinoma of the cervix, randomized patients with bulky stage IB/IIA, or stages IIB – IVA carcinoma of the cervix to extended field radiation therapy versus pelvic radiation therapy with concurrent 5-FU/cisplatin. At a median follow-up of 36 months, overall survival was statistically significantly improved in the group receiving concurrent chemotherapy (75% vs. 63%,  $p=0.0027$ ).<sup>1</sup> In RTOG 9001, a 19% reduction was observed in distant metastases in the arm that received 5-FU and cisplatin. This effect on distant control of disease has not been observed with other chemotherapy regimens in phase III trials; consequently, 5-FU and cisplatin will be utilized in this study.

**1.3.2** Additional large scale, cooperative group, randomized phase III studies have shown a benefit of concurrent chemoradiotherapy in carcinoma of the cervix. Weekly cisplatin concurrent with pelvic radiation therapy has been studied in two randomized phase III GOG trials of patients with cervical carcinoma. As definitive treatment of locally advanced cervical cancer, the regimen was less toxic than a three drug regimen of hydroxyurea, 5-FU, and cisplatin with concomitant radiation and was found to have improved five-year survival rates compared to a regimen with hydroxyurea and radiation.<sup>2</sup> In a GOG trial of concurrent cisplatin and radiotherapy versus radiotherapy alone prior to extrafascial hysterectomy, weekly cisplatin with concomitant radiation therapy resulted in improved disease-free and overall survival.<sup>3</sup>

**1.3.3** Angiogenesis has been linked to increased metastasis formation and decreased overall survival in patients with various tumors, including the uterine cervix.<sup>7-9</sup> Angiogenesis is a unique process by which new blood vessels are formed.<sup>10</sup> Tumors stimulate angiogenesis by directly secreting angiogenic substances or activating and releasing angiogenic compounds stored within the extracellular matrix.<sup>11</sup> Angiogenesis is a prerequisite for tumor growth greater than 1-2 cubic millimeters.<sup>12</sup> Therefore, tumor angiogenesis is a very important therapeutic target.<sup>13-16</sup> Numerous growth factors play a role in angiogenesis including tumor necrosis factor alpha<sup>17</sup>, acidic and basic fibroblast growth factor (*bFGF*)<sup>18,19</sup>, placental growth factor (*PGF*)<sup>20</sup> and vascular endothelial growth factor (*angiogenin or VEGF*).<sup>13,15,21-24</sup>

**1.3.4** Cyclooxygenase (*COX*) is the enzyme that catalyzes the synthesis of prostaglandins (*PGs*) from arachidonic acid. Nonsteroidal anti-inflammatory drugs (*NSAIDs*) inhibit COX-mediated synthesis of

PGs. While cyclooxygenase-1 (*COX-1*) is constitutively expressed in a wide range of tissues, cyclooxygenase-2 (*COX-2*) is cytokine inducible. Enhanced *COX-2* expression has a key role in the development of edema by impeding blood flow and causing immunomodulation that is observed in pathologically altered disease states. *COX-2* is overexpressed in a variety of different tumors, including colon, pancreatic, prostate, lung and head and neck cancers. *COX-2* is also observed within human tumor neovasculature, suggesting that *COX-2* derived prostaglandins contribute to tumor growth by inducing formation of new blood vessels. Celecoxib, a *COX-2* inhibitor, which spares *COX-1* at therapeutic doses in humans, is a potent inhibitor of angiogenesis.<sup>25</sup> Furthermore, celecoxib inhibited neoplastic cells and neoangiogenic vasculature proliferation by 40-60% in these tumors. Celecoxib suppressed the growth and metastasis of Lewis lung carcinoma in C57/BL6 mice. Celecoxib caused at least a 70% decrease in both tumor growth and metastasis. These and other data suggest that *COX-2* dependent angiogenesis plays a major role in development of cancer. The ability of celecoxib to block neoangiogenesis and tumor proliferation, regardless of the expression of the enzyme in the cancer cells, suggests the potential utility of this anti-inflammatory drug in the treatment of human cancer.

- 1.3.5** Ryu et al. evaluated the relationship between tumor invasion and metastasis of uterine cervical cancer and *COX* expression and apoptosis by comparing the protein expression of apoptosis, *COX-1*, and *COX-2* in 36 patients with FIGO stage IB uterine cervical cancer.<sup>26</sup> *COX-2* expression was observed in all tumor tissues and was especially strong in the tumor invasion site. When *COX-2* expression was investigated according to the groups with regard to the presence of lymph node or parametrial involvement, there was a statistically significant difference in staining at the tumor invasion site (*P value* = 0.040) and the tumor stroma (*P value* = 0.028). Work by Gaffney et al. at the University of Utah have confirmed these findings. In 24 patients with cervical cancer treated with radiotherapy, increased expression of *COX-2* correlated with diminished pelvic tumor control and overall survival. (*in press*)
- 1.3.6** Preliminary published results suggest that irradiation upregulates VEGF production in tumor cells, which in turn stimulates tumor angiogenesis. Inhibition of VEGF activity with neutralizing antibodies before irradiation sensitizes vascular endothelial cells to irradiation and leads to a greater than additive radiation response in several human tumor xenografts. Furthermore, the effect of angiostatin is greater when it is administered immediately before individual radiation dose fractions compared to administration over a two-week interval post-irradiation.<sup>27-28</sup> Kishi, Milas and co-workers<sup>29,30</sup> reported that *COX-2* inhibition on tumor improved the response to radiotherapy in an animal model, possibly through an antiangiogenic mechanism. More importantly, this enhancement came without markedly affecting normal tissue radioresponse. Evidence supporting this rationale come from the work of Gallo et al. in which *COX-2* inhibition reduced the synthesis of VEGF165 in A-431 and SCC-9 cell lines *in vitro*.<sup>31,32</sup>
- 1.3.7** Hida et al. reported that NSCLC cyclooxygenase activity and proliferation were inhibited by nonsteroidal anti-inflammatory drugs such as aspirin, indomethacin and ibuprofen.<sup>33</sup> A selective *COX-2* inhibitor, nimesulide, can inhibit proliferation of NSCLC cell lines *in vitro* in a dose-dependent manner, in part by inducing apoptosis. In addition, when used in combination at clinically achievable concentrations, *COX-2* inhibitors reduced the IC50 values of various anticancer agents by up to 77%, although the level of reduction varied considerably. Non-selective NSAIDs inhibit both *COX-1* and *COX-2* protein. *COX-2* specific inhibitors, however, are preferable to non-selective inhibition in that they reduce cancer cell proliferation, induce cancer cell apoptosis and spare *COX-1* induced cytoprotection of the gastrointestinal tract. They suggest that highly selective *COX-2* inhibitors be considered as “adjuncts to various anti-cancer agents for the treatment of high risk patients without compromising their quality of life”.<sup>28</sup>
- 1.3.8** Gene expression utilizing microarray technology has been evaluated in a wide variety of neoplasms.<sup>34-36</sup> Microarray technology allows for the simultaneous evaluation of thousands of genes. In addition, evaluation of tumor specimens for *COX-2*, VEGF, bFGF, MVD, and TUNEL staining for apoptosis prior to treatment and at the time of the first implant will provide powerful insights into the response of particular genes or genetic pathways after therapy with radiation, cisplatin, 5-FU, and celecoxib.

In this study, we will perform microarray testing for gene expression and immunohistochemistry for protein expression prior to treatment and at the time of the first implant. The microarray procedure allows for the simultaneous evaluation of over 20,000 separate gene sequences which have been sequence-verified. This includes over 4,000 known genes. To accomplish these studies, biopsies of the cervix are highly recommended prior to treatment and at the first implant. (8/20/02)

#### **1.4 Celecoxib Pharmacology**

- 1.4.1** Mechanism of Action: Celebrex™ is a nonsteroidal, anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of

Celebrex™ is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2; at therapeutic concentrations in humans, Celebrex™ does not inhibit the COX-1 isoenzyme. In animal tumor models, Celebrex™ reduced the incidence and multiplicity of tumors. In a study of patients with FAP (*Familial Adenomatous Polyposis*), Celebrex™ at 400 mg bid significantly reduced the number of colon polyps. Consequently, for this study, we will use the 400 mg bid dose of Celebrex™. This dose has been utilized in previous studies and was demonstrated to be safe. The length of treatment will be one year.

- 1.4.2** *Pharmacokinetics*: Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels ( $C_{max}$ ) and area under the curve (*AUC*) are roughly dose proportional up to 200 mg b.i.d.; at higher doses, there are less than proportional increases in  $C_{max}$  and *AUC*. Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid, and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.
- 1.4.3** *Safety*: Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomized 12-24 week trials using active comparators, two of which also included placebo controls. Twelve-week endoscopic ulcer data are available on approximately 1,400 patients and 24-week endoscopic ulcer data are available on 184 patients on Celebrex™ at doses ranging from 50-400 mg b.i.d.. In all three studies that included naproxen 500 mg b.i.d., and in the study that included ibuprofen 800 mg t.i.d., Celebrex™ was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period.
- 1.4.4** Celebrex™ should not be given to patients who have demonstrated allergic reactions to sulfonamides. Celebrex™ should not be given to patients who have experienced asthma, urticaria, or allergic reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

## **2.0 OBJECTIVES**

- 2.1** To determine treatment-related toxicity rates in patients with locally advanced carcinoma of the cervix treated by oral Celebrex™, intravenous cisplatin and 5-FU and concurrent pelvic radiation therapy.
- 2.2** To test whether the use of concurrent Celebrex™ and chemoradiotherapy increases locoregional control rates, distant control, disease-free survival, and/or overall survival, and to determine if the patterns of first failure are changed compared to historical controls.
- 2.3** To collect tissue to perform future immunohistochemical analyses for angiogenic markers to correlate with clinical outcome; and to perform future microarray testing for evaluation of gene expression.

## **3.0 PATIENT SELECTION**

### **3.1 Conditions for Patient Eligibility (8/20/02)**

- 3.1.1** Histologic proof of squamous, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix including FIGO (*International Federation of Gynecologists and Obstetricians*) stage IIB to IVA or patients with FIGO stage IB to IIA who have biopsy-proven pelvic node metastases and/or tumor size  $\geq$  5 cm.
- 3.1.2** No evidence of disease outside of the pelvis.
- 3.1.3** Zubrod Performance Status 0-2.
- 3.1.4** Laboratory values must be as follows:
- |                             |   |
|-----------------------------|---|
| White blood cell count:     | $\geq 3,000/\text{mm}^3$                              |
| Absolute granulocyte count: | $\geq 1,500/\text{mm}^3$                              |
| Platelets:                  | $\geq 100,000/\text{mm}^3$                            |
| Total bilirubin:            | $\leq 1.5 \text{ mg/dl}$                              |
| Serum creatinine:           | $\leq 1.5 \text{ mg/dl}$                              |
| AST or ALT:                 | $\leq 2.5 \text{ x institutional upper normal limit}$ |
| Serum calcium:              | $\leq 1.3 \text{ x institutional upper normal limit}$ |
| Creatinine clearance:       | $\geq 50 \text{ cc/min}$ , calculated as follows:     |

For females:

Creatinine clearance (mL/min) =	0.85 x	$\frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}}$
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3.1.5 Signed study-specific informed consent prior to study entry.

**3.2 Conditions for Patient Ineligibility (8/20/02)**

- 3.2.1 Prior or simultaneous malignancies (*other than cutaneous basal cell carcinoma*) unless disease-free > 3 years.
- 3.2.2 Medical illness preventing the use of full-dose chemotherapy.
- 3.2.3 Carcinoma of the cervix with the following histologies: small cell, carcinoid, glassy cell, clear cell, and adenoid cystic.
- 3.2.4 Previous medical or psychiatric illness which would prevent informed consent or limit survival to less than six months.
- 3.2.5 Patients known to be infected with HIV. Patients with HIV may have a pronounced response to radiation therapy. HIV testing is not required for participation in this study.
- 3.2.6 Prior surgery for carcinoma of the cervix other than biopsy.
- 3.2.7 Patients with para-aortic disease. Evaluation of para-aortic lymph nodes can be done by CT or MRI scan of the abdomen/pelvis. All patients with suspicious para-aortic lymph nodes on CT or MRI should have biopsy by fine needle aspirate or surgery.
- 3.2.8 Previous pelvic radiation therapy or systemic chemotherapy is not permitted other than transvaginal irradiation to control bleeding.
- 3.2.9 Patients who have experienced hypersensitivity to Celebrex™, or any component of its formulation. Patients who have demonstrated allergic reactions to sulfonamides, or patients who have experienced asthma, urticaria, or allergic reactions after taking aspirin or other NSAIDS.
- 3.2.10 Patients who have recently been on Celebrex™ or any other COX-2 inhibitor within two months of study entry.
- 3.2.11 Patients taking dilantin and lithium; patients with active cardiac disease. Physicians should carefully review the medications that their patients are taking and consult the PDR since some medications interfere with the metabolism of celecoxib via the cytochrome P450 2C9 pathway.
- 3.2.12 Patients with active GI ulcers, GI bleeding, or inflammatory bowel disease.
- 3.2.13 Pregnant or lactating females. Radiation therapy and cytotoxic agents are contraindicated in pregnancy.

**4.0 PRETREATMENT EVALUATIONS**

**4.1 Mandatory Evaluations (*All pretreatment evaluations must be completed prior to study entry*).**

- 4.1.1 History and physical examination including height, weight, body surface area and Zubrod Performance Status (*ZPS*). Documentation of the nature and size (*including measurements in three dimensions*) of the primary tumor is required. Initial examination should be performed by a gynecologic oncologist and radiation oncologist.
- 4.1.2 All patients will have confirmation of diagnosis by cervical biopsy within six weeks prior to study entry. It is highly recommended that patients have biopsies for fresh tissue acquisition prior to treatment and at the first implant (*see Sections 8.0, 10.2*). (8/20/02)
- 4.1.3 All patients will undergo complete blood count with differential and platelets, BUN, serum creatinine, bilirubin, AST or ALT, calcium, electrolytes, and alkaline phosphatase. Creatinine clearance should be calculated. Laboratory studies must be done within two weeks of study entry.
- 4.1.4 Chest X-Ray within six weeks prior to study entry.
- 4.1.5 CT or MRI of the abdomen/pelvis that must include evaluation of the abdomen to at least the level of the renal vessels with contrast (*IVP is optional*) within six weeks prior to study entry. Conventional CT should be performed with cuts of 10 mm or less in slide thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. MRI is strongly preferred in order to allow tumor measurement in three dimensions.
- 4.1.6 Evaluation of para-aortic lymph nodes is required to at least the level of the renal vessels by contrast-enhanced CT or MRI. All patients with suspicious para-aortic lymph nodes on CT or MRI scan should have biopsy by fine needle aspirate or surgery.
- 4.1.7 Cystoscopy and sigmoidoscopy are suggested for bulky lesions at the discretion of the oncologist and in concert with imaging findings. Negative predictive value for invasion of the urinary bladder on MRI is highly reliable and can be used as a triage point for need for cystoscopy.
- 4.1.8 Pregnancy test for premenopausal women.

4.1.9 Metastatic evaluation as indicated.

## **5.0 REGISTRATION PROCEDURES (9/2/03)**

- 5.1 Each institution must submit a Celebrex™ Shipment Form (*Appendix XIII*) to the CTSU Regulatory Office (215-579-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case (the shipment form is only submitted once). **Canadian Institutions must submit the Site Information Sheet and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** Allow adequate processing time (*7-10 days*) before calling to register your first case.
- 5.2 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 and a case number will be assigned and confirmed by mail. 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.

## **6.0 RADIATION THERAPY**

**Treatment Plan:** Patients will be treated with a combination of external and intracavitary irradiation. Every effort should be made to use intracavitary irradiation. If a patient has distal vaginal involvement, an interstitial implant may be performed. Extensive tumor precluding intracavitary irradiation should be considered for interstitial implantation as the next choice. When brachytherapy is not performed, a detailed explanation should be provided to RTOG Headquarters data management and dosimetry.

### **6.1 External Beam**

Whole pelvis will be treated to a total dose of 45 Gy in 5 weeks. Four-field technique (*AP-PA and lateral opposed fields*) is recommended, particularly when treatment is delivered with a beam energy of < 15 MV. Patients will be treated once a day, 5 days a week with a daily fraction size of 1.8 Gy. A whole pelvic dose of 45 Gy should be delivered. A midline block may be used at the discretion of the treating radiation oncologist. If the patient has extensive tumor which precludes intracavitary treatment, shrinking field techniques should be performed to bring gross tumor volume with adequate margins to a minimum of 65 Gy. The involved lateral parametrium and/or involved pelvic nodes should be boosted with fields tailored to encompass known areas of disease to achieve a total dose (*including the intracavitary treatment*) of 60 Gy  $\pm$  5%. See Section 6.1.4 for parametrial fields.

#### **6.1.1 Physical Factors**

A megavoltage beam of 4 MV or greater, with a minimum source-axis distance of 100 cm and a minimum source-to-skin distance of 80 cm will be used.

#### **6.1.2 Radiation Therapy Fields**

All fields treated require simulation and portal verification on the treatment unit. Copies of these films will be submitted to RTOG Headquarters. At simulation, techniques to limit irradiation of the small bowel should be employed including: simulation and treatment in the prone position and a full bladder. If a four-field technique is used, use of a bellyboard and contrast opacification of the small bowel is recommended. The distal most aspect of cervico-vaginal disease should be marked using radio-opaque seeds at 6 and 12 o'clock positions or using a radio-opaque vaginal tampon. Barium or other radio-opaque treatment device should be used to localize the rectum. The tumor volume including gross nodal disease should be delineated on the simulation films (*AP and lateral projections*) or digitally reconstructed radiographs (*DRR's*) if CT treatment planning is used.

#### **6.1.3 Pelvic Field**

##### **6.1.3.1**

##### AP-PA Portals:

Superior Border: a transverse line between L4 and L5.

Inferior Border: transverse line below obturator foramen or 3 cm below the most distal vaginal disease, to include the introitus if necessary.

Lateral Border: 2 cm lateral to widest true pelvic diameter.

Custom Blocking: to shield small bowel and femoral heads while maintaining a margin of at least 1 cm from common iliac nodes and should not shield the obturator foramina.

##### **6.1.3.2**

##### Lateral Portals:

Superior/Inferior Borders: Identical to AP-PA fields.

Anterior Border: A line drawn anterior to the symphysis pubis and at least 1 cm anterior to common iliac nodes at L4-L5.

Posterior Border: In most cases, the entire sacrum should be included in the lateral fields. Posterior block should be designed so that the gross tumor is encompassed by at least 3 cm margins. In cases with small volume of disease, a line through the posterior sacrum may be used to include the cervical disease with a margin of 3-4 cm. The lateral field border should be placed at the posterior aspect of the L4-L5 vertebral body.

**6.1.4** Reduced Fields: Parametrial/ Nodal Boost (for Stage IIB/IIIB)

**6.1.4.1** Parametrial Boost

AP-PA fields with inferior and lateral borders identical to pelvic fields.

Inferior border: may be the same as the pelvic field or may be brought up to the midobturator foramen.

Superior border: 9-12 cm above inferior border, tailored to the position of the cervix and uterus from radio-opaque markers and intracavitary films. Central blocking should measure at least 4.5 cm at midplane and should be tailored to the position of the intracavitary system.

**6.1.4.2** Nodal Boosts

At least 4x4 cm and maintain a margin of 1-1.5 cm from involved nodes.

**6.1.4.3** Treatment Technique

In general, parametrial and/or nodal boosts will be given with AP-PA ( $\geq 10$  MV) technique. However, other techniques including CT planned fields are acceptable. All fields will be treated on a daily basis.

**6.1.4.4** Dose Specifications

The parametrial and/or nodal boost fields will be treated with 1.8 Gy qd prescribed to Point B (*see Appendix VII*) to bring the cumulative dose (*including initial pelvic fields and contribution from brachytherapy*) to Point B to 60 Gy  $\pm$  5%.

**6.1.5** Radiation Treatment Interruption

Every effort must be made to minimize treatment interruptions. If treatment interruptions are necessary, every effort should be made to achieve the prescribed radiation dose. Follow-up must continue regardless of radiation therapy received.

**6.1.6** Protocol Compliance

Variation from protocol – acceptable:

- Less than one week interruption of external beam radiation therapy;
- External beam radiation therapy final doses vary  $\leq$  10%.

Minor variation:

- One to two week delay in radiation therapy unless there is medical necessity.

Deviation from protocol – unacceptable:

- No chemotherapy;
- Doses of radiation therapy vary more than  $\pm$  10% for external beam radiation therapy;
- Field of radiation therapy is other than pelvic contents (*whole abdomen or para-aortic*);
- Greater than two week delay unless there is medical necessity.

**6.2** Intracavitary Applications

Low dose rate (*LDR*) or high dose rate (*HDR*) brachytherapy can be employed in this study.

**6.2.1** LDR Brachytherapy

Cesium will be used with standard intracavitary systems preferably in two intracavitary applications. An effort should be made to deliver a minimum cumulative external and intracavitary dose to Point A of 85 Gy (*See Appendix VII*). Occasionally, normal tissue tolerance limits may demand a lower dose when vaginal and uterine anatomy does not permit optimal brachytherapy. If tumor and normal tissue anatomy permit acceptable intracavitary geometry, treatment may be performed as soon as the fourth week of external beam therapy. The interval between the two applications will be 1-3 weeks. It is recommended that the total course of treatment be completed in less than 56 days. Interstitial brachytherapy may be used to treat distal vaginal disease that cannot be adequately covered with intracavitary treatment.

**6.2.2** HDR Brachytherapy

**6.2.2.1** For patients receiving HDR brachytherapy, 5 fractions of 6.0 Gy each to Pt. A will be used. See RTOG High Dose Rate Intracavitary Brachytherapy Guidelines (*Appendix VIII*) for guidelines of vaginal surface dose, normal tissue tolerances, packing and imaging.

**6.2.2.2** Timing

HDR brachytherapy may start as early as week three. When HDR brachytherapy begins, at least one insertion will be performed per week with no external beam therapy given on the day of the insertion. If the majority of the external beam radiation has been given, then two insertions per week could be done separated by at least 72 hours in order to complete all treatment within eight weeks.

- 6.2.2.3** HDR Instruments  
It is strongly recommended that tandem and ovoids or a tandem and ring be used for HDR brachytherapy. A tandem and cylinder is allowed only for patients where tandem and ovoid application is not possible due to extent of disease.
- 6.2.3** Intracavitary Radiotherapy Dosimetry
- 6.2.3.1** Intra-uterine tandems and vaginal applicators such as the Fletcher-Suit-Delclos afterloading system is recommended. The dose to points A, B, rectum, bladder and vaginal vault must be calculated and reported.
- 6.2.3.2** Point A: Measure 2 cm along the intrauterine tandem from the cervical os or phlange of the tandem and 2 cm laterally in the plane of the intracavitary system.
- 6.2.3.3** Point B: 5 cm lateral from a point 2 cm vertically superior to the cervical os or phlange of the central tandem.
- 6.2.3.4** Bladder Dose: calculated at the center (*in the superior-inferior plane on A:P view*) of a contrast-filled balloon of a Foley catheter and closest to the applicator system (*posterior balloon surface*) on a lateral view.
- 6.2.3.5** Rectal dose: In accordance with ICRU 38, mark the point 0.5 cm posterior to the vaginal surface at the midpoint of the applicator system.
- 6.2.3.6** Vaginal Surface Dose: calculated at the vaginal surface lateral to the midpoint at the surface of the ovoid.
- 6.2.3.7** Maximum doses to sensitive structures for patients treated with LDR implant: Small Intestine: 55 Gy; Bladder: 75 Gy; Rectum: 70 Gy; Vaginal Surface: 130 Gy.
- 6.2.3.8** Determination of normal tissue tolerance for HDR: In order to stay below an LDR equivalent of 70 Gy to the rectum for five HDR insertions ( $120 \text{ Gy}^3$ ), including the 45 Gy contribution from the external beam radiation, the rectum should receive less than 4.1 Gy for each HDR fraction of 6 Gy (68% of the prescribed dose to Point A). The dose to the bladder should be less than 4.6 Gy per each HDR fraction of 6 Gy (77% of the prescribed dose to Point A). As in LDR brachytherapy, every attempt should be made to deliver tumoricidal doses, even if the late responding tissues receive a slightly higher dose.
- 6.3** Radiation Toxicities
- 6.3.1** Side effects expected from radiation therapy include fatigue, diarrhea, rectal irritation, urinary frequency and dysuria, loss of pubic hair, darkening of skin in the treatment portal, low blood counts. Common long-term effects include vaginal narrowing and shortening and dyspareunia. Long-term side effects, although uncommon, may include rectal bleeding, loose stool, rectal ulcer, dysuria, urinary frequency, hematuria, vaginal vault necrosis. Rare long-term effects include bowel obstruction, ureteral obstruction, vesicovaginal or rectovaginal fistula.
- 6.3.2** All toxicities will be recorded on data collection forms.

## **7.0** DRUG THERAPY

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

### **7.1** Celebrex™

- 7.1.1** Formulation: Celebrex™ is provided as 100 mg or 200 mg capsules to be taken orally. (8/20/02)
- 7.1.2** Storage: Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F).
- 7.1.3** Adverse Effects: Incidence rates of adverse events associated with Celebrex™ are provided in the product package insert. The following events are expected with the administration of Celebrex™:
- 7.1.3.1** Gastrointestinal toxicity: Serious toxicity such as bleeding, ulceration, and perforation can occur with non-steroidal anti-inflammatory drugs (NSAIDS). Upper GI bleeding occurred in 0.04% of patients on controlled clinical trials at a daily dose of 200 mg or more. Patients that are at a higher risk of developing GI side effects include patients with a prior history of GI bleeding and/or peptic ulcer disease. Other therapies or co-morbid conditions that may increase the risk of GI bleeding include: treatment with anticoagulants, longer duration of NSAIDS, smoking, alcoholism, older age, and poor general health status.
- 7.1.3.2** Hematologic toxicity: Anemia has been reported in patients on Celebrex™. Celebrex™ does not generally affect platelet counts, prothrombin time, partial thromboplastin time, and does not appear to inhibit platelet aggregation at indicated dosages.
- 7.1.3.3** Hepatotoxicity: Transient elevations in liver enzymes, especially SGOT (AST), and bilirubin, have been reported.

**7.1.3.4** Anaphylactic-like reactions: Anaphylactic-like reactions may occur in patients previously exposed to NSAIDS. Symptoms include facial edema, wheezing, tachycardia, and hypotension. Very rare cases of anaphylactic reactions and/or angioedema have been reported in patients receiving Celebrex™.

**7.1.4** Supplier: Celebrex™ will be supplied by Pfizer, Inc. in 200 mg capsule form. (8/20/02, 3/15/04)

**7.1.4.1** Celebrex™ Distribution for Canadian Study Sites (3/15/04)

The Celebrex™ supplied for this study will not be used for any other purpose other than for this study or administered other than as described in the protocol.

**Shipments to Canada (9/2/03)**

**Canadian Institutions must submit the Site Information Sheet and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** Pfizer Canada Inc. will ship Celebrex™ from its corporate office in Mississauga, Ontario, to participating Canadian institutions after Pfizer Canada Inc. has received the following documentation from RTOG:

- Ethics committee approval letter clearly identified with protocol title and study-specific consent form, version dated;
- Ethics Committee approved informed consent;
- Completed Site Information Sheet including the drug shipment address;
- Completed Trial Site Information Form and the fax confirmation sheet indicating that it has been filed with the Health Products and Food Branch (HPFB).

An initial drug shipment of 24 bottles of Celebrex (100 capsules per bottle; 200 mg/capsule) will be provided to the institution after Pfizer Canada Inc. has received the appropriate documentation from RTOG. The trial inventory of Celebrex™ at each site should always have sufficient supply for two patients to complete three months of treatment. To request additional supplies of Celebrex™, complete the Request for Trial Drug Shipment Form that is included with your original drug shipment and fax the request to the Pfizer Canada, Clinical Trials Supply Manager at FAX number 905-755-3151. The site pharmacist must confirm the receipt of the Celebrex™, and to comply with this request, the site pharmacist must sign and date the Drug Shipment Invoice and fax the invoice to the Pfizer Canada, Clinical Trials Supply Manager at FAX number 905-755-3151.

**7.1.4.2** Celebrex™ Distribution for U.S. Sites (3/15/04, 5/14/04)

Celebrex™ is manufactured by Pfizer/Searle Corporation and will be supplied free of charge for this study.

**Shipments to U.S. Sites (9/2/03)**

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received using the Drug Accountability Record Form. Celebrex™ will be distributed by Pfizer, Inc.. Each institution must submit the Celebrex™ Shipment Form (*Appendix XIII*) to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. Allow adequate processing time (7-10 days) before calling to register the first case. RTOG will fax the completed Celebrex™ Shipment Form and Celebrex™ Drug Order Request Form (*in forms packet*) to Pfizer, Inc. for the initial drug shipment. An initial drug shipment of 24 bottles of Celebrex (100 capsules per bottle; 200 mg/capsule) will be provided to the institution after Pfizer, Inc. has received the appropriate documentation from RTOG. The trial inventory of Celebrex™ at each site should always have sufficient supply for two patients to complete three months of treatment. Pfizer, Inc. will ship, using two-day express delivery, the requested number of bottles to the institution. Initial shipment will be sent within 15 business days following receipt of the request to Pfizer, Inc.. Subsequent requests for re-supply will be made directly by the institution to Pfizer, Inc. utilizing the Celebrex™ Drug Order Request Forms. The re-supply shipment will be sent within 10 business days. Sites should order enough drug to ensure that an adequate supply is available between shipments. All unused Celebrex™ must be destroyed at the site and documented in the Drug Accountability Record Form.

Additional questions about supply and delivery should be directed to:

Cynthia Barbitsch, RPh  
Sr. Associate Clinical Study Manager  
U.S. Medical Oncology  
Phone:212-733-3664  
Fax:646-441-5602  
cynthia.barbitsch@pfizer.com

- 7.1.5** Administration: Patients will receive 200 mg oral capsules of Celebrex™ for the prescribed dose of 400 mg b.i.d. (*total daily dose of 800 mg*). during external beam radiation therapy (*whole pelvis and parametrial boost*). Celebrex™ will be started on the first day of external radiation therapy (*day 1*), preferably approximately three hours prior to radiation therapy. Celebrex™ will be continued daily for 12 months. All Celebrex™ doses should be taken with food to ensure adequate absorption. A drug prescription or script will be written by the investigator and retained as source documentation for sponsor-supplied drug. The dispensed amount is not to exceed a three- month supply of drug. A new script will be written at each return visit. **(8/20/02)**
- 7.1.6** At weekly intervals during treatment and at each follow-up visit, an assessment of patient drug compliance will be made and recorded in the patient's medical record. Compliance should be recorded as the percentage of pills taken. To help in the assessment of compliance, it is required that patients keep a diary or calendar record of their daily pill consumption. Prior to starting treatment, the patient will be provided with and instructed in the proper use of a pill diary (*see Appendix X for an example*) or a calendar to record their daily pill consumption. The patient will be instructed to return this diary at intervals during treatment and at each follow-up visit. This record will be checked for compliance by the investigator. The diary will be retained in the patient's record for submission to RTOG ONLY upon request; i.e., diaries are not to be submitted but will be retained at the site as source documents. Patients who are non-compliant must be re-instructed in the use of the diary. **(8/20/02)**
- 7.1.7** Upon completion or discontinuation of Celebrex™, the patient must be instructed to return all unused supply to the investigator for proper disposal. **(8/20/02)**
- 7.2** Cisplatin (Platinol®)
- 7.2.1** Formulation: Cisplatin is available as a dry powder supplied in 10 mg and 50 mg vials and in aqueous solution in 50 mg and 100 mg vials with 100 mg mannitol and 90 mg sodium chloride.
- 7.2.2** Preparation: The 10 mg and 50 mg vials should be reconstituted with 10 ml or 50 ml sterile water for injection USP, respectively. Each ml of the resulting solution will contain 1 mg of cisplatin. Reconstitution as recommended results in a clear colorless solution.  
**NOTE:** Aluminum reacts with cisplatin causing precipitation formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.
- 7.2.3** Storage: Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature. The aqueous solution should be stored at room temperature and protected from light. The reconstituted solution is stable for 20 hours at room temperature.  
**NOTE:** Once reconstituted, the solution should be kept at room temperature. If the reconstituted solution is refrigerated, a precipitate will form.
- 7.2.4** Adverse Effects: Incidence rates of adverse events associated with cisplatin are provided in the product package insert. The following events are expected with the administration of cisplatin:
- 7.2.4.1** Nephrotoxicity: Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28-36% of patients treated with a single dose of 50 mg/m<sup>2</sup>. It is first noted in the second week after a dose and is manifested as elevated BUN, creatinine, and serum uric acid, or as a decrease in creatinine clearance. Because renal toxicity becomes more prolonged and severe with repeated courses of cisplatin, renal function must return to normal before another dose can be given.
- 7.2.4.2** Ototoxicity: Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m<sup>2</sup>. It is manifested by tinnitus and/or hearing loss in the high frequency range. Deafness has been reported rarely.
- 7.2.4.3** Hematologic Toxicity: Myelosuppression occurs in 25-30% of patients treated with cisplatin. Nadirs in circulating platelets and leukocytes occur between Days 18 and 23 with most patients recovering by Day 39. Thrombocytopenia, anemia, neutropenia, and fever are also possible adverse events.

- 7.2.4.4** Gastrointestinal Toxicity: Marked nausea and vomiting occur in almost all patients treated with cisplatin. Diarrhea and anorexia have also been reported.
- 7.2.4.5** Neurotoxicity: Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. Neuropathy usually occurs after prolonged therapy (*4 to 7 months*); however, symptoms have been reported after a single dose. Muscle cramps, loss of taste, seizures, autonomic neuropathy, dorsal column myelopathy, and Lhermitte's sign have also been reported.
- 7.2.4.6** Ocular Toxicity: Optic neuritis, papilledema, and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequency than those recommended in the package insert.
- 7.2.4.7** Anaphylactic-like Reactions: Anaphylactic-like reactions have occasionally been reported in patients previously exposed to cisplatin. Symptoms include facial edema, wheezing, tachycardia, and hypotension.
- 7.2.4.8** Hepatotoxicity: Transient elevations in liver enzymes, especially SGOT (AST), and bilirubin, have been reported.
- 7.2.5** Other Toxicities: Other infrequent toxicities that have been reported include cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, and asthenia. Rare cases of local soft tissue toxicity have occurred.
- 7.2.6** Supplier: Commercially available.
- 7.2.7** Administration: Intravenous cisplatin 75 mg/m<sup>2</sup> will be administered on days 1, 22, and 43. One hour before the cisplatin infusion, 500 cc of ¼ or ½ normal saline should be infused intravenously. Increased oral intake should be encouraged starting the day before cisplatin administration. Cisplatin 75 mg/m<sup>2</sup> will be given in 1 liter of D5 ½ normal saline and 50 gm Mannitol and 2 gm MgSO<sub>4</sub> as a 1-2 hour infusion. The cisplatin dose will not exceed 150 mg maximum. Adequate vigorous post-chemotherapy hydration should be given and additional fluids administered as clinically indicated to replace emesis. Standard institutional nausea prophylaxis is encouraged. Renal function should be assessed and cisplatin withheld according to the criteria in Section 7.4.2.2. Cisplatin should not be given during the break, should it occur, between the completion of external beam RT and the initiation of brachytherapy.
- 7.3** **5-Fluorouracil**
- 7.3.1** Formulation: 5-FU is commercially available in 500 mg/10 cc ampules. It is stable if protected from light. If a precipitate is present, it is to be gently heated to no greater than 140°F in a water bath. In aqueous solution it is colorless to faint yellow, and is pH adjusted with sodium hydroxide to 8.6-9.0.
- 7.3.2** Preparation: An infusion pump should be used to control the infusion flow rate. The volume of diluent is dependent upon the particular type of pump used.
- 7.3.3** Storage: 5-FU should be stored at room temperature.
- 7.3.4** Adverse Effects: Toxicities associated with the systemic administration of 5-FU include nausea and vomiting, stomatitis, phlebitis, diarrhea, myelosuppression, alopecia, rash, photosensitivity, cerebellar ataxia (*rare*), and very occasionally angina with accompanying EKG changes. "Hand and foot syndrome" has been observed in patients receiving continuous infusion 5-FU.
- 7.3.5** Supplier: Commercially available.
- 7.3.6** Administration: Cisplatin should be administered within 16 hours of the first radiation fraction. 5-FU will be given by continuous infusion at a dose of 1000 mg/m<sup>2</sup> (*maximum dose 2000 mg*) for 4 consecutive days (*96 hours: total dose 4,000 mg/m<sup>2</sup>*) on days 2-5, 23-26, and 44-47. 5-FU may start within 1 hour after the completion of cisplatin but not more than 36 hours after completion of cisplatin. If the patient is to receive a second LDR brachytherapy treatment, cisplatin and 5-FU will be given at that time as described above with cisplatin given the evening prior to the insertion of the applicator and 5-FU starting when the system is loaded and continuing for the full 96 hours. If a third course of chemotherapy is given, it must be administered no earlier than day 43 of study entry (*a minimum of three weeks after the second course of chemotherapy was started*). If the patient does not have an absolute granulocyte count  $\geq 1000 \text{ mm}^3$  or platelet count  $\geq 75,000 \text{ mm}^3$ , no further chemotherapy will be given and brachytherapy will proceed as indicated.
- 7.4** **Dose Reduction Criteria**
- 7.4.1** Celebrex™: Toxicities that can be attributed to Celebrex™ should have dose modifications as follows: (8/20/02)

### Dose Modification Scheme for Celebrex™

Toxicity*	Grade 2**	Grade 3**	Grade 4**
1st appearance	Interrupt until resolved to grade 0-1, then continue at same dose with prophylaxis where possible	Interrupt until resolved to grade 0-1, then continue at 75% of starting dose***	Discontinue permanently unless investigator deems it to be in the patient's best interest to continue at 50% once toxicity has resolved to grade 0-1
2nd appearance of same toxicity	Interrupt until resolved to grade 0-1, then continue at 75% of starting dose***	Interrupt until resolved to grade 0-1, then continue at 50% of starting dose	
3rd appearance of same toxicity	Interrupt until resolved to grade 0-1, then continue at 50% of starting dose	Discontinue treatment permanently	
4th appearance of same toxicity	Discontinue treatment permanently		

\*CTC Version 2.0 except for grading of hand-foot syndrome

\*\*For patients with Grade 2-4 toxicities during chemoradiation, Celebrex™ may be withheld until the completion of chemoradiation.

\*\*\*When modified for toxicity to a 75% dose adjustment for a total daily dose of 600 mg, administer 400 mg in AM (2 –200 mg capsules) and 200 mg (1-200 mg capsule) in PM.

#### 7.4.2 Cisplatin

7.4.2.1 A patient with grade 2 or greater platinum-related neuropathy will not receive further cisplatin.

7.4.2.2 In addition, Cisplatin dose modification will be based on renal toxicity as follows:

Maximum serum creatinine (mg/dl) in a well-hydrated state with two readings	Dose Modification
< 1.5	No change in cisplatin dose
1.6 to 2.0	Decrease cisplatin dose 50% (to 35 mg/m <sup>2</sup> )
> 2.0	Hold cisplatin (re-evaluate the following week)

#### 7.4.3 5-Fluorouracil

7.4.3.1 Patients who develop one of the following toxicities will have interruption of both chemotherapy and radiation therapy for one week. When resumed, 5-FU dose will be reduced by 50%. Should the toxicity recur, no further 5-FU will be given to that patient. If a greater than one week delay is required for recovery, no further 5-FU will be given when RT is resumed:

WBC < 1500/mm<sup>3</sup> or absolute granulocyte count < 500/mm<sup>3</sup>, platelets < 75,000/mm<sup>3</sup>;

Grade 4 nausea or diarrhea (a grade 4 nausea that resolves within 48 hours of cisplatin administration will not delay therapy or change dosage);

The development of grade 3-4 stomatitis/pharyngitis or Grade 3 hand/foot syndrome, will result in the discontinuation of 5-FU for 3 to 5 days; however, there will be no interruption of radiation. When resumed, there will be a 50% reduction in 5-FU dosage. Hand/foot syndrome (*palmer-plantar erythrodysesthesia*) is an uncommon subacute toxicity that may be dose-limiting. Please notify Dr. Miller with any questions regarding hand/foot syndrome.

Although not expected in this treatment regimen, cardiac-related chest pain will result in the permanent discontinuation of 5-FU.

#### 7.4.4 Dose Modification of Cisplatin and 5-Fluorouracil for Neutropenic Fever

Neutropenic fever (temperature of 38.5° with AGC < 1000) is an expected potential complication of concurrent chemotherapy and radiotherapy. If neutropenic fever is noted after the first or second course of chemotherapy, there should be a 20% reduction of cisplatin to 60 mg/m<sup>2</sup> and 20% reduction of 5-Fluorouracil to 800 mg/m<sup>2</sup>. If neutropenic fever recurs after the initial dose reduction for course #2, the reduction should be 50% for cisplatin to 35 mg/m<sup>2</sup> and 50 % for 5-Fluorouracil to 500 mg/m<sup>2</sup> for course #3.

### 7.5 Adverse Reaction Reporting

7.5.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP Home page

<http://ctep.info.nih.gov>. All appropriate treatment areas should have access to a copy of the CTC version 2.0. This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

**7.5.2** The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents.

- Any unexpected (*not listed in the package label*), life threatening (*Grade 4*) or unexpected, fatal (*Grade 5*) adverse event with an attribution of possible, probable or definite should be reported in *five (5)* working days. The AE should be reported on the FDA Form 3500 MedWatch (*available from the FDA -www.fda.gov/medwatch.*) **(8/20/02)**

- The completed form should be forwarded to the FDA:  
**MedWatch**  
**5600 Fishers Lane**  
**Rockville, Maryland 20852-9787**  
**Fax: (800) 332-0178**

- A copy should be forwarded to the NCI:  
**Investigational Drug Branch**  
**P.O. Box 30012**  
**Bethesda, Maryland 20824**  
**Fax: (301) 402-1584**

**7.5.3** Within 24 hours of discovery, the AE should be telephoned to RTOG Headquarters Data Management, and to the Study Chairman; the report should be sent to RTOG, FDA, and IDB within five (5) working days. **(8/20/02)**

**7.5.4** Any death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery.

**7.5.5** Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at <http://ctep.info.nih.gov>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed within 30 days of AML/MDS diagnosis to the address on the form and to the RTOG Data Management Department:

Investigational Drug Branch (NCI/CTEP) P.O Box 30012 Bethesda, MD 20824	and	RTOG Headquarters AML/MDS Report 1101 Market Street, 14 <sup>th</sup> floor Philadelphia, PA 19107
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## **7.6 Serious Adverse Event (SAE) Reporting for Pfizer, Inc. (8/20/02, 3/15/04)**

### **7.6.1 Definition of Adverse Event**

All serious adverse events, regardless of relationship to study drugs, must be reported to RTOG in an expedited manner (*see next section for reporting instructions*).

A serious adverse event (SAE) is any adverse event that:

- 7.6.1.1** Results in death;
- 7.6.1.2** Is life-threatening;
- 7.6.1.3** Requires inpatient hospitalization or prolongation of existing hospitalization (*excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care*);
- 7.6.1.4** Results in persistent or significant disability or incapacity.
- 7.6.1.5** Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-

threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

If the investigator becomes aware of an SAE that occurs (*regardless of relationship to study drug*) within 30 days after stopping protocol therapy (*i.e. after last dose*) or more than 30 days after stopping protocol therapy, and is considered related to protocol therapy, the SAE must be reported in accordance with procedures specified in this protocol.

**7.6.2** Serious Adverse Event Reporting Instructions

All serious adverse events must be reported as follows:

Within 24 hours (*of investigator knowledge of event*) report event by faxing the FDA 3500 form to Medwatch and:

RTOG Data Management  
1101 Market Street, 14<sup>th</sup> floor  
Philadelphia, PA 19107  
1-800-227-5463 Ext. 4189  
Fax: 215-928-0153

Investigational Drug Branch (NCI/CTEP)  
P.O. Box 30012  
Bethesda, MD 20824  
301-230-2330  
Fax: 301-230-0159

If necessary, the initial report is to be followed by submission of more detailed adverse event information on the same FDA 3500 form within 5 working days of the event.

**7.6.2.1** RTOG Headquarters Reporting Responsibilities for U.S. Sites (3/15/04)

All serious adverse events must be reported as follows:

RTOG will forward by fax a copy of all serious adverse events occurring at U.S. sites, regardless of relationship to protocol treatment, to Pfizer, Inc. within 24 hours of receipt by RTOG.

Please report SAE's using the Serious Adverse Event Fax Coversheet. This form includes information for faxing to Pfizer, Inc. and must accompany the MedWatch form when faxed to Pfizer, Inc.. The following information must be included: 1. protocol number 2. causality 3. date report was submitted to the FDA.

Reporting Information:

To: U.S. Pharmacovigilance  
Fax: 1-616-337-9477 Phone: 1-800-253-8600

**7.6.2.2** RTOG Headquarters Reporting Responsibilities for Canadian Sites (3/15/04)

All serious adverse events must be reported as follows:

RTOG will forward by fax a copy of all serious adverse events occurring at Canadian study sites, regardless of relationship to protocol treatment, to Pfizer Canada Inc., within 24 hours of receipt by RTOG. (*Note: Only those SAE's that occur at Canadian sites should be reported to Canadian Pharmacovigilance*).

Please report SAE's using the Serious Adverse Event Fax Coversheet. This form includes information for faxing to Pfizer and must accompany the MedWatch form when faxed to Pfizer. The following information must be included: 1. protocol number 2. causality 3. date report was submitted to the FDA.

Reporting Information:

Drug Safety Unit  
Pfizer Canada Inc.  
555 Standish Court, Suite 1200  
Mississauga, Ontario L4W 5J5  
FAX: 800-353-0942  
Phone: 888-391-2222 toll free

The Therapeutic Products Directorate (TPD) of the Canadian Health Protection Branch will be notified in an expedited manner of serious adverse events considered unexpected and related to protocol treatment. In addition, the RTOG will inform all investigators of all serious adverse events reported to TPD and request that local ethics boards (REB/IRB/IEC) be notified of the same.

#### **7.6.2.3** Reporting Serious Adverse Events to Local Ethics Boards

Investigators must notify their Research Ethics Boards (REB/IRB/IEC) of any serious adverse events sent by RTOG for the purpose of reporting to REBs (*as outlined in previous section*). Documentation from the REB of receipt of these reportable serious adverse events must be kept on file in the centre.

### **8.0** SURGERY (8/20/02)

To perform the biologic endpoints, > 300 mg of cervical tumor tissue is highly recommended both prior to treatment and at the time of the first implant. Usually, this amount of tissue can be obtained with three passes of a Tischler biopsy forceps. The sample should be placed in RNAlater™ for microarray analysis and immunohistochemistry, and mailed via overnight mail to the RTOG Tissue Bank (*see Section 10.1.5*). In select patients, a core biopsy, Novak endometrium suction curette, or a Kevourkian-Youngue endocervical biopsy curette may be more appropriate secondary to location of tumor.

### **9.0** OTHER THERAPY

No other NSAIDS are allowed while on protocol treatment.

### **10.0** PATHOLOGY

#### **10.1** RTOG Tissue Bank (Pre-study)

**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.

#### **10.2** RTOG Tissue Bank (ON-study)

**10.2.1** After the patient has been registered on the study, the participating institution will call Amy Furness at LDS Hospital (*Section 10.1.5*) to obtain the RNAlater™ media. Institutions must have documentation of IRB approval and the RTOG case number before requesting the media from LDS Hospital. Two vials of RNAlater™ and instructions will then be mailed overnight to the requesting institution. One vial will be used for tissue collection prior to treatment, and the other vial will be used for tissue collection at the time of the first implant.

**10.2.2** The following must be provided:

**10.2.2.1** Fresh tumor tissue obtained by cervical biopsy prior to treatment and before the first implant will be placed into the media “RNAlater™” and shipped to the RTOG Tissue Bank for future analysis. Analysis will consist of microarray testing for evaluation of gene expression and immunohistochemical analysis for angiogenic markers to correlate with clinical outcome. See Appendix IX for shipping and handling instructions.

**10.2.2.2** A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank. **(5/19/03)**

**10.2.3** RTOG will reimburse submitting institutions \$100 per case if proper materials (*see Sections 10.1.2.1, 10.1.2.2*) are submitted. RTOG Administration will prepare the proper paperwork and send a check to your institution after confirmation from LDS Hospital that they have received the appropriate number of slides/blocks. RTOG will reimburse an additional amount to those submitting institutions for each biopsy sample received at the RTOG Tissue Bank for microarray testing (*see Section 10.2.2.1*). **(8/20/02)**

**10.2.4** Patient consent form should give the pathologist/investigator authority and responsibility to comply with this request (*pathology specimens belong to the patient from whom tissue has been removed*).

10.2.5 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**

10.2.6 The patient's specimen must be scheduled to arrive at LDS Hospital ONLY at a time when the lab is open. Do not mail any specimen so that it is scheduled to arrive on days or at times when the lab is closed, e.g., holiday, weekends, or after hours. This requirement may impact on the scheduling of the biopsy or may require additional preparation or processing to preserve the specimen. Call the LDS Hospital if contingencies are not covered by these instructions. (8/20/02)

**10.2.7 11.0 PATIENT ASSESSMENTS**

**11.1 Study Parameters (8/20/02)**

Study Parameters	Pre-treatment	Every week during RT	Prior to each course of CDDP and 5-FU	Prior to each brachytherapy procedure	F/U every 3 months to year 2	F/U every 4 months year 3	F/U every 6 months years 4-5	F/U yearly > 5 years
History and PE	X				X <sup>f,g</sup>	X <sup>f,g</sup>	X <sup>f,g</sup>	X <sup>f,g</sup>
ZPS	X							
Physical exam	X	X <sup>f</sup>		X <sup>g,h</sup>				
Tumor staging and biopsy	X <sup>a,e</sup>			X <sup>e</sup>				
Chest X-ray <sup>h</sup>	X <sup>a</sup>							
CT/MRI of pelvis/abdomen <sup>h</sup>	X <sup>a</sup>							
Para-aortic lymph node evaluation	X <sup>a</sup>							
CBC/differential/platelet count	X <sup>b</sup>	X <sup>d</sup>	X					
BUN, creatinine, total bilirubin, AST and/or ALT, alk phosphatase, calcium, electrolytes, calc. creat clearance	X <sup>b</sup>		X <i>creatinine, BUN, ALT, alk phos, total bili, (calc. creat. clearance<sup>i</sup>)</i>					
Pregnancy test <sup>c</sup>	X <sup>b</sup>							
Toxicity Assessment		X	X <sup>j</sup>		X <sup>j</sup>	X	X	X
Tumor response					X	X	X	X

- a. Within six weeks prior to study entry.
- b. Within two weeks prior to study entry.
- c. All women of childbearing age.
- d. Every week during RT and chemotherapy.
- e. Repeat biopsy prior to first brachytherapy procedure (*optional*). (8/20/02)
- f. Radiographic studies as indicated.
- g. Laboratory studies as indicated.
- h. Also at one month following radiation therapy.
- i. As needed.
- j. Acute toxicities related to Celebrex<sup>TM</sup>.

## **11.2 Evaluation During Therapy**

- 11.2.1** Weekly clinical examination including pelvic assessment and measurement. Radiographic studies will be performed as clinically indicated.
- 11.2.2** Weekly complete blood count, platelet count and differential.
- 11.2.3** Serum chemistry including creatinine, BUN, ALT or AST, alkaline phosphatase, bilirubin, will be performed prior to each dose of cisplatin and 5-FU.
- 11.2.4** Physical examination including pelvic assessment and measurement will be performed prior to each brachytherapy procedure and one-month following the completion of radiation therapy; repeat biopsy will be done prior to first brachytherapy procedure.

## **11.3 Evaluation of Response and Toxicity**

- 11.3.1** *Response*: Patients will be followed for disease status and for the appearance of chronic toxicity with history, physical examination, and indicated laboratory and radiological tests as follows:
- First and second years post therapy: every 3 months
  - Third year post therapy: every 4 months
  - Fourth and fifth years post therapy: every 6 months
  - Annually thereafter.
- Recurrent tumor should be documented histologically when ever possible.
- 11.3.2** *Toxicity*: Myelosuppressive toxicity: lowest observed WBC, granulocyte and platelet count. Anemia and red cell transfusions will be documented. Renal and hepatic toxicity will be reported as changes in BUN, creatinine, ALT, total bilirubin and alkaline phosphatase.

## **11.4 Criteria For Response**

- 11.4.1** *Complete Clinical Response*: Disappearance of all clinical evidence of active tumor for a minimum of four weeks.
- 11.4.2** *Partial Clinical Response*: Fifty percent or greater decrease in the product of the diameters of the measured cervical lesion.
- 11.4.3** *Stable Disease*: No change in the tumor size (<25 % decrease or <25% increase).
- 11.4.4** *Progressive Disease*: ≥ 25% increase in the size of the measured lesion or the appearance of new metastatic lesions.

## **11.5 Criteria For Discontinuing Study Treatment**

- 11.5.1** Progressive disease as defined in Section 11.4.4.
- 11.5.2** The development of unacceptable treatment toxicity.
- 11.5.3** Patient request.

## **12.0 DATA COLLECTION**

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

### **12.1 Summary of Data Submission (8/20/02)**

<b><u>Item</u></b>	<b><u>Due</u></b>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pre-Study Pathology Report (P1)	
Pre-Study Pathology Blocks/Slides (P2)	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription ( <i>Protocol Treatment Form</i> ) (T2)	
Films ( <i>simulation and portal</i> ) (T3)	
Calculations (T4)	
<u>Final Dosimetry Information:</u>	Within 1 week of RT end
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Boost Films ( <i>simulation and portal</i> ) (T8)	
Intracavitary Dose Form (I9)	For Implant #1
Intracavitary Films (T0)	
Intracavitary Dose Form (I9)	For Implant #2
Intracavitary Films (T0)	

Radiotherapy Form (T1)	Within 1 week of RT end
Initial Follow-up Form (FS)	At day 90 or week 13
Treatment Form (TF)	At end of first, second, and third cycles. Final at termination.
Follow-up Form (F1)	Every 3 months from treatment start to year 2; q 4 months year 3; q 6 months years 4-5, then annually. Also at progression/relapse and at death
Autopsy Report (D3)	As applicable

## **12.2 Site Records**

Site records must contain details regarding dosage, and start and stop dates of Celebrex™ treatment. These records include documentation of tracking treatment compliance, e.g., medical record notes, notations of telephone calls to patient, patient diaries, etc., and must include the patients prescriptions/scripts for Celebrex™. (8/20/02)

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints**

#### **13.1.1 Primary Endpoint**

Treatment-related toxicity (*as defined below*) in patients with locally advanced carcinoma of the cervix treated by oral Celebrex™, cisplatin and 5-FU and concurrent pelvic radiation therapy:

- grade 3 nausea, vomiting or diarrhea, despite medical intervention
- grade 4 neutropenia or leukopenia which persist for > 7 days or febrile neutropenia defined as a temperature  $\geq 38.5^{\circ}\text{C}$  and granulocytes  $<1000/\text{mm}^3$
- grade 3 hematological toxicity with exception of neutropenia and leukopenia
- grade 3 other toxicity including GI, renal, cardiac, pulmonary, hepatic, and neurological toxicity

#### **13.1.2 Secondary Endpoints**

- Treatment completion and compliance
- Local regional control (*pelvic control*)
- Distant control
- Disease-free survival
- Overall survival
- To collect tissue to perform future immunohistochemical analyses for angiogenic markers to correlate with clinical outcome; to collect tissue to perform future microarray testing for evaluation of gene expression.

### **13.2 Sample Size**

Based on the experience from RTOG 90-01, about 22% of patients in the chemoradiation arm experienced the toxicities defined in Section 13.1.1. Assuming 20% of the toxicity is considered tolerable, we consider a toxicity rate of 35% or above as excessive.

Seventy-five evaluable cases will be entered to the study unless the accrual is stopped prematurely (*see interim analysis for early stopping*). With 75 evaluable cases, we have 5% chance of rejecting the treatment when the severe toxicity rate is 20%, and 90% chance of rejecting the treatment when the severe toxicity rate is 35%. Considering 10% ineligible or lack-of-data cases, **the total sample size is 83.**

### **13.3 Accrual Duration**

Based on accrual statistics from RTOG 90-01, it is expected that RTOG will enter about 5 cases per month. Thus, the accrual should be completed in approximately one and a half years. If the accrual falls below two cases per month, the feasibility of continuing this study will be discussed at the Research Strategy Committee.

### **13.4 Follow-up**

To determine the efficacy of the treatment and the secondary endpoints, a minimum of two years of follow-ups after the closure of the accrual is needed to estimate two-year results.

### **13.5 Analysis Plan**

**13.5.1** Interim Reports

Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about

- patient accrual rate with projected completion date;
- pretreatment characteristics of patients accrued;
- compliance rate of treatment per protocol;
- the frequencies and severity of toxicity due to chemotherapy and radiation therapy.

**13.5.2** Interim Analysis for Early Stopping (8/20/02)

The first interim analysis for excessive toxicity will be performed after 15 evaluable patients have been entered and have finished their protocol chemotherapy treatment. If we observe 13 or more cases with severe toxicity in the first 15 cases, we may conclude that the treatment is too toxic. The second interim analysis will be performed when 43 evaluable patients have been entered and have finished their protocol chemotherapy treatment. If we observe 23 or more cases with severe toxicity in the first 43 cases, we may conclude that the treatment is too toxic. If any fatal treatment morbidity occurs, it will be immediately reviewed by the study chair, followed by a conference call with all study chairs to determine if a dose modification is warranted. If there are two such fatal treatment morbidities, accrual will be immediately suspended pending review by the study chairs.

**13.5.3** Analysis of Toxicity After Full Accrual (8/20/02)

This analysis will be performed upon the completion of the treatment of the final patient entered to the study. The number of patients will be tabulated by the type and grade of toxicity and the grading of protocol treatment compliance. If we observe 34 or more cases with the toxicities defined in Section 13.1.1, we will reject treatment due to excessive toxicity.

**13.5.4** Analysis of the Treatment Efficacy

The efficacy analysis of the treatment will be delayed to one to two years after the initial treatment toxicity analysis. The two-year probability of local-regional failure and distant failure will be reported using the cumulative incidence approach.<sup>37</sup> A two-year overall survival will also be computed using the Kaplan-Meier method.<sup>38</sup>

**13.6** Inclusion of Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, the possible difference in any of the above endpoints among the racial groups will be investigated. Summary statistics such as percentage of minorities entered, estimates of the endpoints by the racial groups will be reported. Based on accrual statistics from RTOG 90-01, the following table provides the projected number of patients for each racial group.

**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	3	21	17	2	37	3	83

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## **APPENDIX I**

### **RTOG C-0128**

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

##### **STUDY TITLE**

##### **A PHASE I/II STUDY OF COX-2 INHIBITOR, CELEBREX™ (*CELECOXIB*) AND CHEMO-RADIATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL 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 cervical cancer.

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

The purpose of this study is to find out what effects (good and bad) radiation and chemotherapy combined with the drug Celebrex™ have on improving the chance of cure from your cancer. The use of Celebrex™ for cervical cancer is a new treatment. This study will also see how well this treatment regimen can be tolerated.

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

About 83 women will take part in this study.

##### **WHAT IS INVOLVED IN THE STUDY? (8/20/02)**

If you take part in this study, you will receive external radiation therapy once daily (Monday to Friday) for five weeks. You will receive three cycles of chemotherapy in your vein (i.v.). This will be done at three week intervals starting at the time of radiation. One of the drugs (cisplatin) will be given i.v. as a one to two hour infusion on days 1, 22, and 43. The other drug (5-FU) will be given by continuous i.v. over 4 days starting the day after the cisplatin on days 2-5, days 23-26, and days 44-47. In general, this can be done as an outpatient at your institution. When you start radiation, you will also take a drug called Celebrex™. This pill is taken two times per day for twelve months. On days when you receive radiation therapy, it should be taken three hours before you receive

radiation therapy. You should take Celebrex™ with food to make sure that it is absorbed properly.

After your external radiation treatments are finished, you will have either two or five radioactive implants placed into the tumor. Before the first implant, another biopsy will be done (optional). These implants are part of the standard therapy for cervical cancer. Additional external radiation may or may not be given after that. Your doctor will discuss this with you.

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

**Prior to study entry:**

- History and physical examination
- Tumor biopsy
- Chest X-ray
- CT/MRI scan of the abdomen or pelvis
- Lymph node evaluation
- Blood tests
- Pregnancy test (if applicable)

**Prior to study treatment:**

- Biopsy (optional, but highly recommended)

**Every week during treatment:**

- Physical examination
- Blood tests

**Before each dose of cisplatin and 5-FU:**

- Blood tests

**Prior to first implant:**

- Biopsy (optional, but highly recommended)

**During follow-up:**

- Physical examination every 3 months to year two; every 4 months year 3; every 6 months years 4-5; yearly after 5 years
- Laboratory and X-ray studies as needed

Also, at the time of your diagnosis by biopsy, some of your tumor was removed. As is usually done, this tissue went to the hospital pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department and some samples were sent to a central office for review. In this study, you are being asked for permission to have an additional biopsy prior to treatment and at the time of the first implant. These biopsies are optional. The biopsy is a small piece of tissue (about the size of a pea) obtained from the cervix. This

tissue will be sent to a central office for review and research investigation associated with this protocol.

Investigators are hoping to learn if certain proteins and genes are “turned on” or “turned off” with your cancer treatment. They may also learn what makes tumors more aggressive and what makes tumors respond to treatment.

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

The study treatment will take 12 months to complete. Follow-up visits will be scheduled every three months for two years, then every four months for year three, every six months for years four and five, and then yearly for the rest of your life.

The researcher may decide to take you off this study if it is in your best medical interest, your condition worsens, or new information becomes available and this information suggests that the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be dropped 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 chemotherapy and radiation are stopped, but in some cases side effects can be serious or long-lasting or permanent.

#### **Risks Associated with Radiation Therapy to the Pelvis including Implants:**

##### Very Likely:

- Decrease in blood counts which can lead to a risk of infection and bleeding
- Fatigue
- Diarrhea
- Rectal irritation
- Urinary frequency and painful urination
- Loss of pubic hair
- Darkening of skin
- Vaginal narrowing and shortening
- Painful intercourse

Less Likely, But Serious

- Rectal bleeding
- Rectal ulcer
- Blood in urine
- Bowel obstruction
- Ureteral obstruction
- Vaginal vault destruction
- Abnormal opening between bladder/vagina or rectum/vagina

Young women will go through the change of life. Medication will be given to help with their symptoms.

Reproductive risks: Radiation to the pelvis will cause sterility and you will not be able to become pregnant. If you are nursing your baby, you should not do so while on this study.

**Risks Associated with Cisplatin**

Very Likely

- Decrease in blood counts which can lead to a risk of infection and bleeding.
- Loss of appetite and/or taste; metallic taste in your mouth
- Nausea and/or vomiting
- Fatigue
- Hearing loss or ringing in the ears
- Numbness or tingling in the hands or feet

Less Likely

- Muscle cramps or spasm
- Loss of coordination
- Involuntary movements or shaking

Less Likely, But Serious

- Loss of muscle or nerve function which may cause weakness or numbness in your hands and feet
- Facial swelling
- Decreasing ability of the kidneys to handle the body's waste which may be permanent
- Allergic reactions which can cause difficulty in breathing, fast heartbeat, and sweating
- Decrease in liver function causing temporary elevations in blood tests
- Other cancer called Acute Leukemia

## **Risks Associated with 5-FU (5-Fluorouracil)**

### Very Likely

Decrease in blood counts which can lead to a risk of infection and bleeding  
Loss of appetite  
Nausea and/or vomiting  
Diarrhea with cramping or bleeding  
Skin rash  
Fatigue  
Headaches  
Hair loss which is temporary  
Mouth sores  
Sore throat

### Less Likely

Confusion  
Inflammation of the fingers and toes  
Increased sensitivity to sunlight  
Darkening of the skin, nails, or veins  
Loss of coordination or balance  
Inflammation of the veins  
Loss of coordination

### Less Likely, But Serious

Chest pain which may cause damage to the heart

## **Risks Associated with Celebrex™ (8/20/02)**

### Very Likely

Upset stomach

### Less Likely

Elevation of liver blood tests  
Increase in chloride in blood  
Decrease in potassium in blood  
Skin rash  
Nausea, fatigue, lethargy  
Jaundice  
Diarrhea  
“Flu-like” symptoms  
Excessive weight gain

Less Likely, But Serious

Anemia  
Fluid retention or swelling  
Bleeding from the stomach  
Ulceration  
Allergic reaction  
Shortness of breath  
Chest pain

**Risks Associated with Blood Drawing**

You may experience some discomfort, bruising and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

**Risks Associated with Repeat Biopsy**

Less Likely

Bleeding, infection

Less Likely, But Serious

Pelvic discomfort  
Abnormal opening between bladder/vagina or rectum/bladder

**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 cervical 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; (3) surgery; or (4) 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 of applicable drug manufacturers, and other groups or organizations that have a role in this study.

## **WHAT ARE THE COSTS? (8/20/02)**

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. The Celebrex™ will be provided to you by the drug company at no cost to you while you are on the study.

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.

## **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.

**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 (8/20/02)**

**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

\_\_\_\_\_  
Principal Investigator Signature

\_\_\_\_\_  
Date

**TISSUE AND BLOOD TESTING (C-0128)(8/20/02)**

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

Yes     No

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

\_\_\_\_\_  
Date

\_\_\_\_\_  
Principal Investigator Signature

\_\_\_\_\_  
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 CERVIX CANCER (AJCC, 1997)

##### TNM CATEGORIES

##### Primary Tumor (T)

TNM	FIGO	DEFINITION
<b>TX</b>	-	Primary tumor cannot be assessed
<b>T0</b>	-	No evidence of primary tumor
<b>Tis</b>	<b>0</b>	Carcinoma <i>in situ</i>
<b>T1</b>	<b>I</b>	Cervical carcinoma confined to uterus ( <i>extension to corpus should be disregarded</i> )
<b>T1a</b>	<b>IA</b>	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions-even with superficial invasion-are T1b/IB. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
<b>T1a1</b>	<b>IA1</b>	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread.
<b>T1a2</b>	<b>IA2</b>	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less.
<b>T1b</b>	<b>IB</b>	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2.
<b>T1b1</b>	<b>IB1</b>	Clinically visible lesion 4.0 cm or less in greatest dimension.
<b>T1b2</b>	<b>IB2</b>	Clinically visible lesion more than 4.0 cm in greatest dimension.
<b>T2</b>	<b>II</b>	Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina
<b>T2a</b>	<b>IIA</b>	Tumor without parametrial invasion
<b>T2b</b>	<b>IIB</b>	Tumor with parametrial invasion
<b>T3</b>	<b>III</b>	Tumor extends to the pelvic wall, and/or involves the lower third of the vagina, and/or causes hydronephrosis or nonfunctioning kidney
<b>T3a</b>	<b>IIIA</b>	Tumor involves lower third of the vagina, no extension to pelvic wall
<b>T3b</b>	<b>IIIB</b>	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney

**APPENDIX III (continued)**  
**STAGING FOR CERVIX CANCER**  
**(AJCC, 1997)**

<b>T4</b>	<b>IVA</b>	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis ( <i>Bullous edema is not sufficient evidence to classify tumor as T4</i> )
<b>M1</b>	<b>IVB</b>	Distant Metastasis

**Regional Lymph Nodes (N)**

<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>NI</b>	Regional Lymph node metastasis

**Distant Metastasis (M)**

<b>MX</b>	Distant metastasis cannot be assessed
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis

**STAGE GROUPING**

Stage 0	Tis	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T1	N1	M0
	T2	N1	M0
	T3a	NI	M0
	T3b	Any N	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 supercede 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**

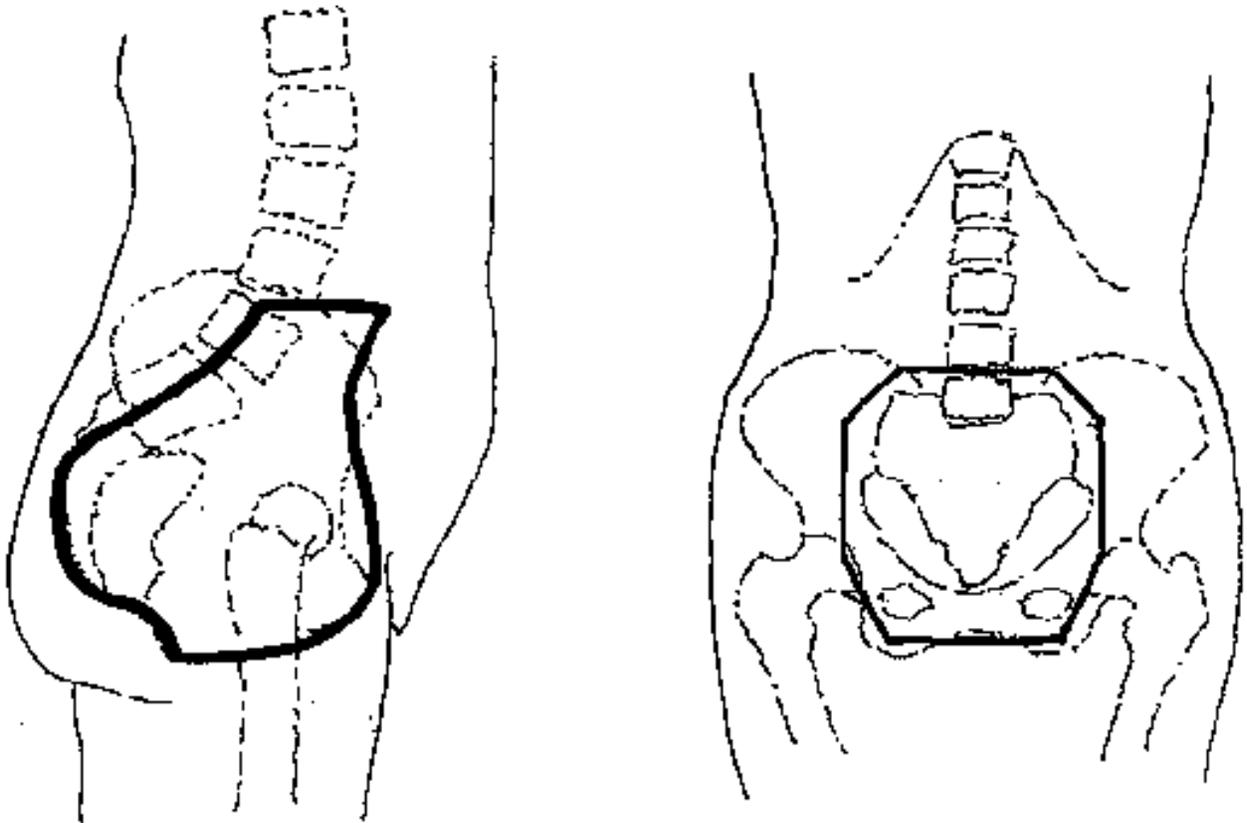
Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

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

APPENDIX VI (p.1)

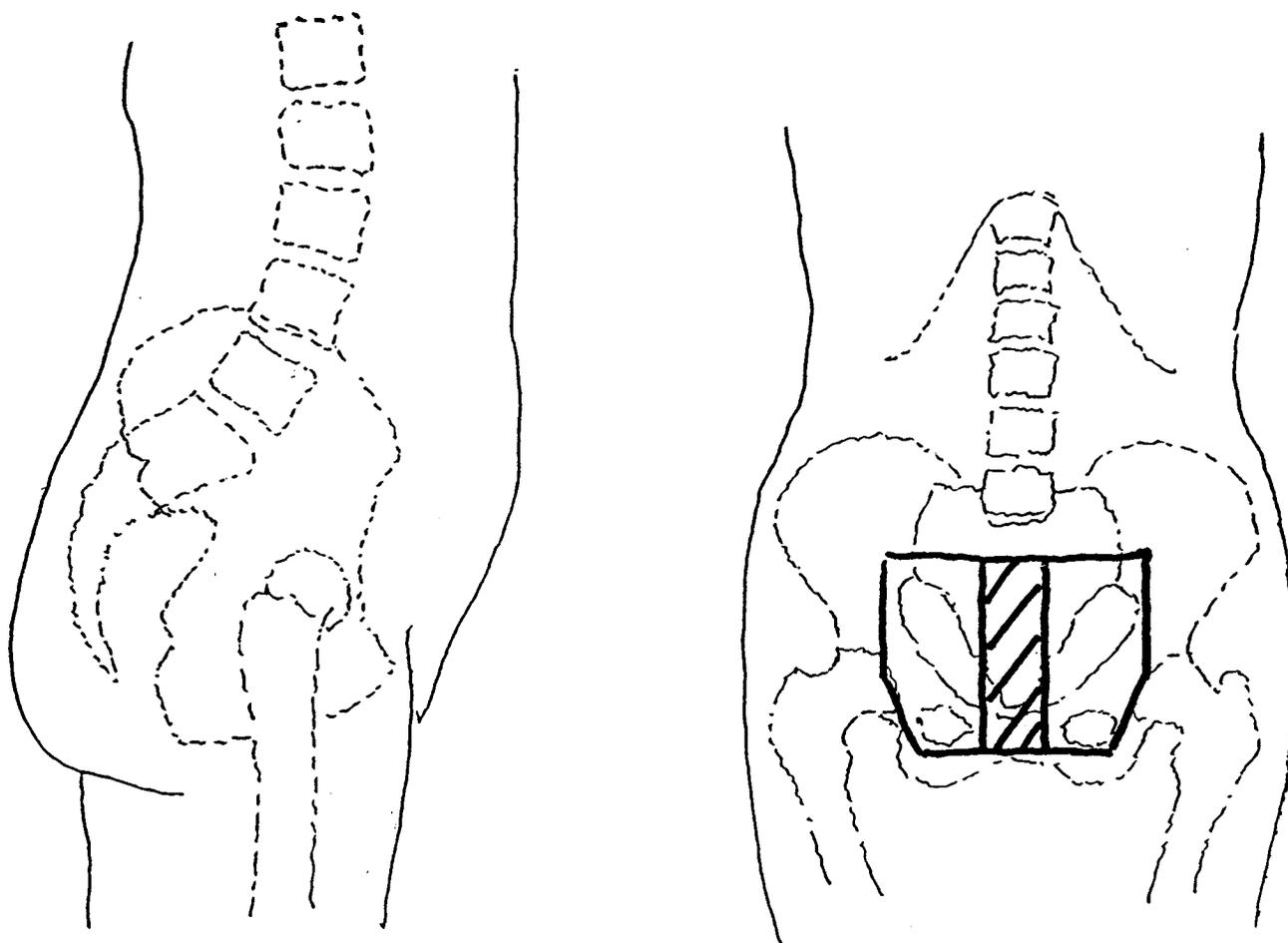
**Sample Treatment Diagram**

**Whole Pelvis**



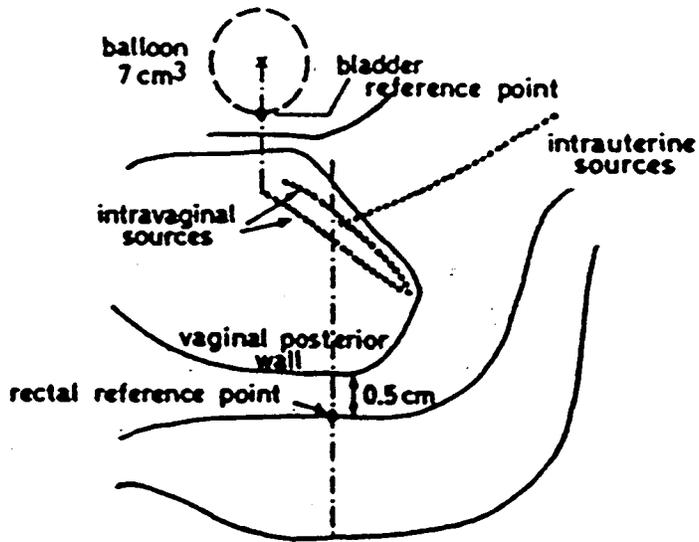
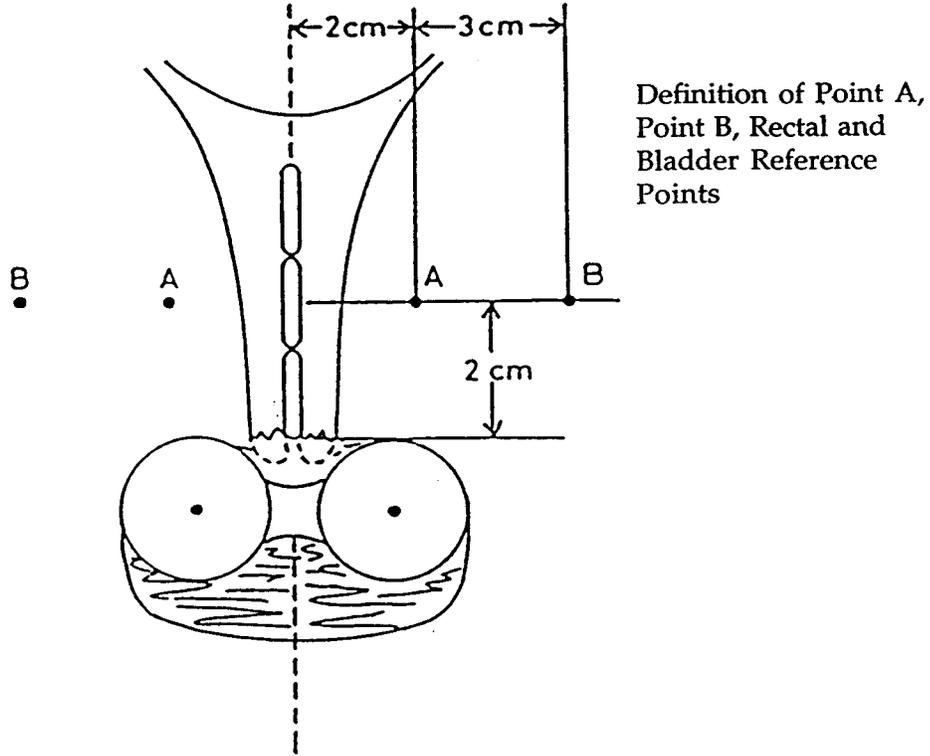
**Sample Treatment Diagram**

**Parametrial Boost with 5-6 cm Midline Shield**



APPENDIX VII

ICRU #38 Point Dose Definition



## **APPENDIX VIII**

### **HIGH DOSE RATE INTRACAVITARY BRACHYTHERAPY GUIDELINES\***

#### **Schedule**

1. HDR brachytherapy may begin at a minimum whole pelvic dose of 1800cGy for favorable vaginal geometry. If vaginal geometry is not favorable, the first HDR insertion should be performed after 4 weeks of external beam (3600 cGy). (If a midline block is used, other acceptable fractionation schemes are shown in Table 1).
2. HDR procedures can be performed once or twice per week with a minimum separation of 2 days. It is important to avoid prolongation of the overall treatment time beyond 56 days. Whether one or two HDR fractions are given per week, the external beam irradiation to the whole pelvis should not be given the same day as the HDR fraction.

#### **Dose Specification**

1. Localization orthogonal x-rays of the applicator system should be obtained for each fraction for dosimetry calculations and dose optimization with and without rectosigmoid contrast.
2. Dose per fraction for the HDR brachytherapy course will be specified at POINT A.
3. The vaginal surface dose shall be defined opposite the dwell positions in each ovoid at a distance equal to the radius of the ovoid. For the ring applicator, the surface dose points on the ring are measured 6 mm laterally from each dwell position on each side of the ring. For the tandem and cylinder, the dose will be calculated at the cylinder surface which generally has a radius between 1.0 and 1.5 cm.
4. Normal tissue dose points will include 1 or 2 rectal dose points based on rectal contrast. A point adjacent to the applicator system or at 0.5-1.0 cm posterior to the vaginal applicator in the lateral projection has previously been described in the RTOG protocols. Alternatively 1 or 2 points may be specified adjacent to the column of barium in the rectum closest to the vaginal applicator as well as by the ICRU rectal point (5mm posterior to the posterior vaginal wall as defined by speculum, barium-soaked packing rectal retractor, or most posterior ovoid, ring, or cylinder position. Bladder dose may be calculated at a point on the surface of a contrast-filled balloon of a Foley catheter closest to the system on a lateral view. Two sigmoid points should also be measured as defined by contrast where the sigmoid crosses the tandem on AP and lateral films.

#### **Brachytherapy Dose** *(The brachytherapy dose in this study will be 6.0 Gy in 5 fx to Pt. A)*

1. The dose to point A will be based on the external beam dose (see Table 1).
2. The vaginal surface dose should be approximately 140% of the Point A dose.
3. Maximum doses to the bladder, rectum, and sigmoid should be less than 70% of the Point A dose.

#### **Treatment Data Requirements**

1. AP and lateral x-rays with and without rectosigmoid contrast of each brachytherapy fraction are required.
2. Copies of dosimetry and computer data for each brachytherapy fraction are required.

**Table 1-Equivalent Doses for Tumor and Late Effects for Doses of EBRT and HDR Brachytherapy used in Cervical Cancer**

EBRT (Gy) @ 1.8 Gy/fx	# of HDR fractions	HDR dose /fx
19.8	7	6.7
19.8	6	7.4
39.6	5	6.6
39.6	6	5.8
45	5	6.0-6.5**
45	6	5.3-5.8**
50.4	4	7.0*
50.4	5	6.0*
50.4	6	5.3*

\*\*these doses are used in treating larger, more advanced tumors

\*Nag S, Erickson B, Thomadsen B, et al. The American Brachytherapy Society recommendations for high dose rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2000;48(1):201-211.

**APPENDIX IX**

**SPECIMEN SUBMISSION FOR MICROARRAY ANALYSIS**

1. RNAlater™ will be obtained by calling Amy Furness at LDS Hospital. Institutions must have documentation of IRB approval and the RTOG case number before requesting the media from LDS Hospital. Two vials containing the media RNAlater™ and instructions will be mailed overnight to the institution. One vial will be used for tissue collection prior to treatment, and one vial will be used for tissue collection at the time of the first implant. RNAlater™ is a preservative that prevents degradation of mRNA (*other solutions including formalin will not suffice*). This solution is essential for the microarray analysis of gene expression; the immunohistochemistry will be obtained from these tissues as well.
2. Obtain 300 mg of cervix tissue prior to treatment and at the time of the first implant. In general, this requires three passes with a Tischler biopsy forceps. In select patients, a core biopsy, Novak endometrium suction curette, or a Kevourkian-Young endocervical biopsy curette may be more appropriate secondary to location of tumor.
3. Place fresh tissue in RNAlater™ solution and mail overnight to the RTOG Tissue Bank at LDS Hospital. A Pathology Submission Form must be included and must clearly state that the material is being submitted to the RTOG Tissue Bank. RTOG will reimburse submitting institutions an additional amount per case if proper materials are submitted. RTOG Administration will prepare the proper paperwork and send a check to your institution after confirmation from LDS that they have received the proper materials. The patient consent form should give the investigator authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*). (8/20/02, 5/19/03)

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**

**Note:** The patient's specimen must be scheduled to arrive at LDS Hospital ONLY at a time when the lab is open. Do not mail any specimen so that it is scheduled to arrive on days or at times when the lab is closed, e.g., holiday, weekends, or after hours. This requirement may impact on the scheduling of the biopsy or may require additional preparation or processing to preserve the specimen. Call the LDS Hospital if contingencies are not covered by these instructions. (8/20/02)

**APPENDIX X (8/20/02)**

**PATIENT'S PILL DIARY**

**INSTRUCTIONS TO THE PATIENT:**

1. Complete one form for each month.
2. Record the date and number of pills each time you take them in the morning and in the evening.
3. Please return the forms to your physician when you go for your follow-up appointments.

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

Patient's Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Physician's Office will complete this section:

1. Please indicate which month of treatment is indicated on this form (1-36): \_\_\_\_\_
2. Complete dates: Start date \_\_\_\_\_ End date \_\_\_\_\_
3. Total number of pills taken this month \_\_\_\_\_

Physician/Nurse/Data Manager's Signature \_\_\_\_\_

**APPENDIX XI (8/20/02)**

**DRUG SUPPLY PROCEDURE FOR CELEBREX™ - CANADIAN SITES (8/20/02)**

**Initial Drug Shipment (3/15/04):**

<i>Site study coordinator</i>	<ul style="list-style-type: none"><li>• Sends originals of the trial site regulatory documents to the Radiation Therapy Oncology Group (RTOG) Registration/Randomization Department</li></ul>
<i>RTOG Registration/Randomization Department</i>	<ul style="list-style-type: none"><li>• Informs the Therapeutic Area Manager at Pfizer Canada Inc. of local trial site activation by faxing (FAX number: 905-890-8522 the following documentation: Ethics Committee approval letter Ethics Committee approved Informed Consent Site Information Sheet Completed Clinical Trial Site Information Form and the fax confirmation sheet indicating that it has been filed with HPFB</li></ul>
<i>Pfizer Canada Inc. Therapeutic Area Manager or designee, Medical Marketing/Clinical Research(MMCR)</i>	<ul style="list-style-type: none"><li>• Completes the request for initial trial drug shipment (Celebrex™). Forwards the request for initial trial drug shipment to the Clinical Trial Supplies Manager.</li></ul>
<i>Pfizer Canada Inc. Clinical Trials Supplies Manager</i>	<ul style="list-style-type: none"><li>• Requests the Clinical Research Coordinator, MMCR, to notify the trial site of the shipment.</li><li>• Ships the following supplies to the trial site pharmacist. The initial shipment will supply enough study drug for 3 months of treatment for 2 patients.<ol style="list-style-type: none"><li>1. 24 bottles of Celebrex™ (100 capsules per bottle; 200 mg capsules)</li></ol></li></ul>
<i>Pfizer Canada Inc. Clinical Research Coordinator, MMCR</i>	<ul style="list-style-type: none"><li>• Notifies the study site pharmacist and coordinator of the shipment by fax.</li><li>• Sends the following documents by courier to the study site pharmacist:<ol style="list-style-type: none"><li>1. Investigational Medication Distribution Forms (drug accountability log)</li><li>2. Additional trial drug request forms</li><li>3. Product monographs: Celebrex™</li></ol></li></ul>
<i>Trial site pharmacist</i>	<ul style="list-style-type: none"><li>• Confirms receipt of the trial drugs by signing and dating the Drug Shipment Invoice that accompanies the trial drug supplies.</li><li>• Sends a signed/dated copy of the Drug Shipment Invoice to the Clinical Trial Supplies Manager, Pfizer Canada Inc. at FAX number 905- 755-3151.</li></ul>

**Requests for trial drug resupply:**

<i>Trial site pharmacist</i>	<ul style="list-style-type: none"> <li>• Manages trial drug inventory ensuring sufficient supplies are maintained for 3 months of treatment for 2 patients</li> <li>• Completes the request for trial drug shipment on an “as needed” basis, depending upon patient accrual.</li> <li>• Sends the request for trial drug shipment to the Pfizer Canada Inc. Clinical Trial Supplies Manager at FAX number 905- 755-3151 .</li> </ul>
<i>Pfizer Canada Inc. Clinical Trial Supplies Manager</i>	<ul style="list-style-type: none"> <li>• Forwards the request to the Therapeutic Area Manager, MMCR.</li> </ul>
<i>Pfizer Canada Inc. Therapeutic Area Manager, MMCR</i>	<ul style="list-style-type: none"> <li>• Approves and signs the request for trial drug shipment.</li> <li>• Forwards the request for trial drug shipment to the Clinical Trial Supplies Manager.</li> </ul>
<i>Pfizer Canada Inc. Clinical Trial Supplies Manager</i>	<ul style="list-style-type: none"> <li>• Ships drug supplies to the trial site.</li> <li>• Requests the Clinical Research Coordinator, MMCR to notify the trial site of the shipment.</li> </ul>
<i>Pfizer Canada, Clinical Research Co-ordinator, MMCR</i>	<ul style="list-style-type: none"> <li>• Notifies the trial pharmacist and site study coordinator of the shipment by fax.</li> </ul>
<i>Trial site pharmacist</i>	<ul style="list-style-type: none"> <li>• Confirms receipt of the trial drugs by signing and dating the Drug Shipment Invoice that accompanies the trial drug supplies.</li> <li>• Sends a signed/dated copy of the Drug Shipment Invoice to the Clinical Trial Supplies Manager, Pfizer Canada @ FAX number (905) 755-3151.</li> </ul>

**Return of trial drug supplies:**

<i>Pfizer Canada Inc. Clinical Research Co-ordinator, MMCR</i>	<ul style="list-style-type: none"> <li>• Forwards the “Return of Clinical Supplies” form to the trial site.</li> <li>• Sends written instruction to the trial site regarding shipment of returned goods to Pfizer Canada offices for destruction.</li> </ul>
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**APPENDIX XII (8/20/02)**

**RTOG C-0128/COXAON-0509-055**

**SITE INFORMATION SHEET – CANADIAN SITES**

To facilitate the timely receipt of drug shipments, supplies and correspondence, we ask that you complete and promptly return this form to RTOG by faxing 215-574-0300. Your careful attention to the accuracy of this form will ensure the correct delivery of all items associated with this clinical trial.

<b>INVESTIGATOR:</b>	
<b>INSTITUTION/ORGANIZATION:</b>	
<b>ADDRESS:</b>	
<b>CITY/PROVINCE:</b>	
<b>POSTAL CODE:</b>	
<b>PHONE NUMBER:</b>	<b>FAX NUMBER:</b>
<b><u>SUB-INVESTIGATOR(S):</u></b>	
<b><u>ADDRESS ( if different form Investigator):</u></b>	
<b>PHONE NUMBER:</b>	<b>FAX NUMBER:</b>
<b><u>SUB-INVESTIGATOR(S):</u></b>	
<b><u>ADDRESS ( if different form Investigator):</u></b>	
<b>PHONE NUMBER:</b>	<b>FAX NUMBER:</b>

<b><u>PHARMACIST:</u></b>	
<b><u>ADDRESS ( if different form Investigator):</u></b>	
<b>PHONE NUMBER:</b>	<b>FAX NUMBER:</b>
<b><u>STUDY COORDINATOR:</u></b>	
<b><u>ADDRESS (if different form Investigator):</u></b>	
<b>PHONE NUMBER:</b>	<b>FAX NUMBER:</b>
<b>INSTITUTIONAL REVIEW BOARD</b>	
<b>NAME:</b>	
<b>ADDRESS (IF DIFFERENT FORM INVESTIGATOR):</b>	

**APPENDIX XIII (8/20/02, 5/19/03, 9/2/03)**  
**RTOG C-0128/COXAON-0509-055**

**A PHASE I/II STUDY OF COX-2 INHIBITOR, CELEBREX™ (CELECOXIB), AND CHEMORADIATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER**

**CELEBREX™ SHIPMENT FORM - U. S. SITES**

Each institution must submit this form (*Appendix XIII*) to the CTSU Regulatory Office (215-579-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case. Allow adequate processing time (*7-10 days*) before calling to randomize your first patient.

**SHIP TO:**

Pharmacist Name: \_\_\_\_\_

Pharmacist Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Pharmacist Phone: \_\_\_\_\_

Pharmacist Fax: \_\_\_\_\_

RTOG Institution Number: \_\_\_\_\_

Institution Name: \_\_\_\_\_

IRB Approval Date: \_\_\_\_\_

*(attach copies of IRB approval and sample consent form)*

Investigator (*PI*) Signature \_\_\_\_\_

Date: \_\_\_\_\_

Investigator Name (*Print*) \_\_\_\_\_

Investigator NCI # (*Required*) \_\_\_\_\_

*Return to:*  
*CTSU Regulatory Office*  
*1818 Market Street, Suite 1100*  
*Philadelphia, PA 19103*  
**FAX 215-569-0206**

RTOG Headquarters Approval \_\_\_\_\_

Date: \_\_\_\_\_