

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG 0524

### A PHASE I/II TRIAL OF A COMBINATION OF PACLITAXEL AND TRASTUZUMAB WITH DAILY IRRADIATION OR PACLITAXEL ALONE WITH DAILY IRRADIATION FOLLOWING TRANSURETHRAL SURGERY FOR NON-CYSTECTOMY CANDIDATES WITH MUSCLE-INVASIVE BLADDER CANCER

NCI-supplied agent: trastuzumab (NSC 688097, IND 6667)

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#### RTOG Headquarters/Department of Statistics

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The following Cooperative Groups have endorsed this trial: ECOG and SWOG

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

**This study is supported by the NCI Cancer Trials Support Unit (CTSU) [1/9/07]**

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

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

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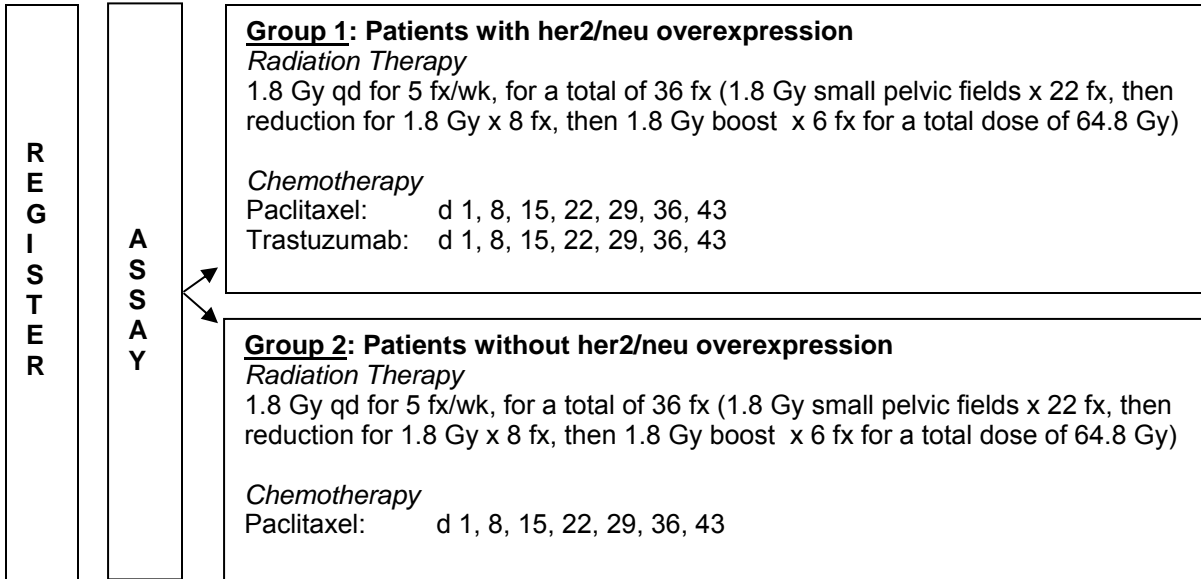
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RTOG 0524

A PHASE I/II TRIAL OF A COMBINATION OF PACLITAXEL AND TRASTUZUMAB WITH DAILY IRRADIATION OR PACLITAXEL ALONE WITH DAILY IRRADIATION FOLLOWING TRANSURETHRAL SURGERY FOR NON-CYSTECTOMY CANDIDATES WITH MUSCLE-INVASIVE BLADDER CANCER

SCHEMA



Note:

Radiation may be started on Monday, Tuesday, or Wednesday.

Chemotherapy may be started on Monday, Tuesday, or Wednesday and should be given on the same day ( $\pm$  1 day) each week. Regardless of the day of the week, the starting date of paclitaxel  $\pm$  trastuzumab should correspond to the first day of radiation therapy

**Patient Population** (See Section 3.0 for Eligibility)

- Patients with transitional cell carcinoma of the bladder
- AJCC stages T2-T4a, NX, N0 or N1, and M0; OR stage T1, grade 3/3
- Patients must have undergone as thorough a transurethral resection of the bladder (TURB) tumor as is safely possible
- There must be sufficient tumor tissue available for her2/neu analysis

**Required Sample Size: 88**

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

RTOG 0524

**ELIGIBILITY CHECKLIST-STEP 1 (7/26/05) (02/24/09) (8/12/09)**

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

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- \_\_\_\_\_ (Y) 1. Is there histological or cytological confirmation of transitional cell carcinoma (TCC) of the bladder with histologic evidence of *muscularis propria* invasion OR stage T1, grade 3/3 as described in Section 3.1.5?
- \_\_\_\_\_ (Y) 2. Has the patient been judged to be medically inappropriate for radical cystectomy?
- \_\_\_\_\_ (Y) 3. Has the patient undergone as thorough a transurethral resection of the bladder tumor (TURB) as is judged safely possible?  
\_\_\_\_\_ (Y) Was bimanual examination by a urologist performed, with tumor mapping as specified in Appendix V?
- \_\_\_\_\_ (Y) 4. Is there sufficient tumor tissue available for her2/neu analysis?  
\_\_\_\_\_ (Y) Will a tumor block be submitted to the RTOG Biospecimen Resource for her2/neu analysis as detailed in Section 10.0?
- \_\_\_\_\_ (Y) 5. Based upon the results of the cystoscopy, TURB, and other clinical radiographic studies, is the primary bladder TCC stage (according to the AJCC 6<sup>th</sup> edition): T2-T4a, Nx, N0 or N1; and M0 **or** T1 with TCC grade 3/3 and felt to require definitive local therapy?
- \_\_\_\_\_ (N) 6. Does the patient have distant metastasis?
- \_\_\_\_\_ (Y) 7. Were a history and physical examination including vital signs and body surface area performed within 4 weeks prior to registration?
- \_\_\_\_\_ (Y) 8. Were a chest x-ray or chest CT scan and an abdominal/pelvic CT scan performed within 8 weeks prior to registration?
- \_\_\_\_\_ (Y/N) 9. Is there clinical evidence of nodal disease?
- \_\_\_\_\_ (0,1,2) 10. What is the Zubrod performance status?
- \_\_\_\_\_ ( $\geq 18$ ) 11. What is the patient's age?
- \_\_\_\_\_ ( $\geq 1800$ ) 12. What is the absolute neutrophil count obtained within 2 weeks prior to registration?
- \_\_\_\_\_ ( $\geq 100,000$ ) 13. What is the platelet count within 2 weeks prior to registration?
- \_\_\_\_\_ ( $\geq 8.0$ ) 14. What is the hemoglobin obtained within 2 weeks prior to registration?
- \_\_\_\_\_ ( $\leq 3.0$ ) 15. What is the serum creatinine?
- \_\_\_\_\_ ( $< 2.0$ ) 16. What is the serum bilirubin?

**(continued on next page)**



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

RTOG 0524

**ELIGIBILITY CHECKLIST-STEP 1 (7/26/05)**

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

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**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 Initials (First Middle Last) (If no middle initial, use hyphen.)
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Race
- \_\_\_\_\_ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- \_\_\_\_\_ 11. Gender
- \_\_\_\_\_ 12. Patient's Country of Residence
- \_\_\_\_\_ 13. Zip Code (U.S. Residents)
- \_\_\_\_\_ 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
- \_\_\_\_\_ 17. Medical Oncologist
- \_\_\_\_\_ (Y/N) 18. Tissue/Blood kept for cancer research?

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

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

Date \_\_\_\_\_

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

RTOG 0524

**ELIGIBILITY CHECKLIST-STEP 2 (7/26/05)**

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

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(assigned for Step 1)

- \_\_\_\_\_ 1. Name of institutional person registering this case
- \_\_\_\_\_ (Y/N) 2. Is the patient going to receive protocol treatment?  
\_\_\_\_\_ If no, the reason the patient cannot continue to Step 2: 1) progression of disease; 2) patient refusal; 3) physician preference; 4) failure to submit tissue assay; 5) other
- \_\_\_\_\_ 3. **If no, call RTOG HQ to “discontinue” the case: provide reason** \_\_\_\_\_  
(progression, patient refusal, physician preference, no tissue submitted, other specify \_\_\_\_\_)
- \_\_\_\_\_ 4. Patient’s Initials
- \_\_\_\_\_ 5. Verifying Physician
- \_\_\_\_\_ 6. Patient’s ID number
- \_\_\_\_\_ 7. Calendar Base Date (for Step 2)
- \_\_\_\_\_ 8. Registration Date (for Step 2)
- \_\_\_\_\_ 9. Results of tissue assay: 1) patient has her2/neu overexpression; 2) patient does not have her2/neu overexpression
- \_\_\_\_\_ 10. Treatment Assignment

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

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background (9/7/05)**

The RTOG and other institutions worldwide have completed numerous studies over the past twenty years proving that selective bladder preservation is an appealing alternative to radical cystectomy for the treatment of muscle-invasive bladder transitional cell carcinoma (TCC).<sup>1-7</sup> The most effective approaches to selective bladder preservation involve a multidisciplinary strategy with transurethral bladder tumor resection (TURB), chemoradiotherapy, and adjuvant chemotherapy. In recent analyses, such an approach results in approximately 50% long-term disease-free survival, comparable to results from contemporary surgical series.<sup>3,8</sup> Most studies in bladder preservation protocols have included only patients who were appropriate candidates for radical cystectomy, and indeed patients were referred for salvage cystectomy if the bladder preservation approach did not result in complete response. Approximately two thirds of patients in RTOG protocols were able to complete the treatment program with an intact and well-functioning native bladder. Recent reviews have described the various approaches and outcomes in greater detail.<sup>3,9,10</sup>

Many patients treated for muscle-invasive bladder cancer are poor-risk patients for surgery, due either to comorbid illness, advanced age, or personal preference. None of the prior RTOG protocols have included such patients, since salvage cystectomy would not be feasible. However, given the overall success of bladder preservation therapy, we believe that nonsurgical treatments can safely be offered to these poor-risk patients, with a reasonable chance for success. The safety and efficacy of this approach has not yet been studied in poor-risk patients.

An important radiosensitizing chemotherapy agent, cisplatin, has been used in most prior protocols. This agent carries a significant risk of nephrotoxicity, which is partially ameliorated by the use of aggressive pre- and post-hydration. Nevertheless, patients with compromised renal function cannot safely receive cisplatin, and the population of patients with TCC tends toward impaired renal function. Alternative radiosensitizing agents have been identified, both in TCC and in other malignancies, and taxanes in particular are effective and safe in this capacity. Two prior RTOG protocols (RTOG 0233 and RTOG 99-06) have safely utilized paclitaxel in conjunction with bladder irradiation. Since paclitaxel is metabolized in the liver, poor renal function is not a contraindication for its use. In a pilot study conducted in 36 patients considered poor-risk for cisplatin therapy, paclitaxel was used in combination with radiation therapy. Paclitaxel was administered twice weekly at 30 mg/m<sup>2</sup>, while radiation was given in 5 fractions of 1.8 Gy each week to a maximum dose of 56.0 ± 3.7 Gy. Twenty-nine patients received the complete chemotherapy course, while 7 required reduction in chemotherapy or discontinuation of treatment, in most cases due to diarrhea. Fourteen patients developed grade 1-2 enteritis, and 9 developed grade 3 enteritis. Other toxicities were minimal, including anemia, nausea, and elevated creatinine. Of 26 patients who underwent restaging cystoscopic examination at the completion of treatment, 22 achieved complete response. Overall 3-year survival was 40% in this population of poor-risk patients.<sup>11</sup>

The role of neoadjuvant chemotherapy in muscle-invasive TCC has not been fully defined despite many randomized trials. However, a randomized study of neoadjuvant chemotherapy in conjunction with bladder preservation therapy demonstrated no benefit in terms of response rate or survival and added to the toxicity of therapy.<sup>12</sup> Subsequent protocols in the RTOG have included adjuvant chemotherapy, although the benefit of adjuvant chemotherapy also is not proven in TCC. Off protocol, most patients with poor-risk health features are not treated with adjuvant chemotherapy.

The role of the epidermal growth factor receptors (EGFRs) in a variety of malignancies has been studied extensively in recent years.<sup>10,11</sup> The FDA has recently approved the use of trastuzumab, a monoclonal antibody against EGFR2 or her2/neu, for appropriate breast cancer patients, and the use of ZD1839, an inhibitor of EGFR1, for selected lung cancer patients. In breast cancer, overexpression of her2/neu is associated with poor prognosis, and the activity of trastuzumab unequivocally correlates with overexpression of her2/neu.<sup>13,15</sup> Numerous studies have investigated expression of her2/neu in bladder cancer using immunohistochemistry and have

found overexpression in 40%-80% of tumors.<sup>16-28</sup> There are conflicting data on relationship of expression with response to treatment and clinical outcome, with a recent RTOG study pointing to a poorer prognosis in patients with TCC who overexpress her2/neu.<sup>29</sup> Thus, targeting this receptor in initial therapy of muscle-invasive bladder cancer may increase complete response and ultimately improve overall survival in patients with her2/neu overexpressing tumors.

This study will assess the safety and efficacy of coadministration of weekly paclitaxel and trastuzumab in combination with daily irradiation in patients with muscle-invasive bladder cancer who are not candidates for radical cystectomy. In patients without her2/neu overexpression, treatment will consist of weekly paclitaxel alone in combination with daily irradiation. Chemoradiotherapy will be preceded by TURB to the fullest extent possible. Assignment of patients to the paclitaxel and trastuzumab group versus the paclitaxel alone group will be based on her2/neu overexpression in the resected tumor samples. Following chemoradiation, response will be with another cystoscopic examination and biopsy. Adjuvant chemotherapy will not be offered as a standard part of the protocol due to the nature of the patient population enrolled in the study and the lack of definitive evidence of a benefit.

In trials of women with breast cancer, treatment with trastuzumab has been associated with a risk of reduction in cardiac ejection fraction. From these studies, cardiac impairment with trastuzumab is strongly associated with past or concurrent anthracycline exposure.<sup>30</sup> In a study of 222 women who had received prior chemotherapy, single-agent treatment with trastuzumab resulted in reduction of ejection fraction in 4% of women, all of whom had either prior anthracycline exposure or known heart disease.<sup>31</sup> In a phase 3 study of chemotherapy (either adriamycin/cyclophosphamide [AC] or paclitaxel [P]) alone or chemotherapy plus trastuzumab (T), cardiac dysfunction was observed in 1% (P), 7% (AC), 11% (P+T), and 28% (AC + T) of women.<sup>13</sup> Thus, trastuzumab should generally not be administered with anthracyclines or in patients with preexisting cardiac disease. For the purposes of this study, designed specifically for non-surgical candidates, mild, asymptomatic LV dysfunction will be permitted, but patients with prior anthracycline exposure will not be allowed. Given that there will be a relatively short duration of trastuzumab therapy, and no anthracycline exposure, an LV ejection fraction of 40% or greater will be allowed.

## **1.2. Biomarkers in Bladder Cancer (9/7/05)**

In addition to her2/neu, other biomarkers might have useful prognostic information for patients with TCC, including EGFR1, p53, p21, pRb, p16, and bcl2.<sup>32-36</sup> The current study will continue the efforts of the RTOG genitourinary translational research program by collecting tissue (archived from TURB specimens after formalin fixation in paraffin blocks and by collecting fresh tumor tissue for genomic studies in RNA<sub>later</sub><sup>TM</sup>). These samples will ultimately be assayed for other biomarkers of interest, defined by new research and/or therapeutic rationale guided by the development of novel biologic agents or small molecules. Analysis of her2/neu will be required in real time in order to assign patients to the correct chemotherapy group. Overexpression of her2/neu in the bladder tumors will not be a requirement for patient entry into the study but will affect chemotherapy assignment. We anticipate that about half of the tumors will overexpress her2/neu, and the study may provide insight into whether this is an important factor in predicting response to therapy in TCC.

## **2.0 OBJECTIVES**

### **2.1 Primary**

**2.1.1** To determine the acute toxicity ( $\leq$  90 days from protocol treatment start) from chemoradiotherapy including paclitaxel  $\pm$  trastuzumab and irradiation in non-cystectomy patients with or without her2/neu overexpression.

### **2.2 Secondary**

**2.2.1** To determine the ability of patients with bladder cancer who are non-cystectomy candidates to complete this treatment program.

**2.2.2** To evaluate the efficacy of this treatment program in achieving a complete response of the primary tumor.

**2.2.3** To measure the 5-year disease-free and overall survival of patients with bladder cancer treated with TURB followed by chemoradiotherapy.

- 2.2.4 To estimate the value of tumor and/or serum biomarkers as predictors of initial tumor response and recurrence-free survival.

### **3.0 PATIENT SELECTION**

#### **3.1 Conditions for Patient Eligibility (9/7/05)**

- 3.1.1 (8/12/09) Pathologically (histologically or cytologically) proven diagnosis of primary bladder transitional cell carcinoma with histologic evidence of *muscularis propria* invasion **OR** patients with stage T1, grade 3/3 as described in Section 3.1.5.
- 3.1.2 Patients must be judged to be medically inappropriate for radical cystectomy.
- 3.1.3 Patients must have undergone as thorough a TURB by a participating urologist as is judged safely possible. Bimanual examination by a participating urologist must have been performed, with tumor mapping as specified in Appendix V. (See Section 4.1.3)
- 3.1.4 There must be sufficient tumor tissue available for her2/neu analysis.
- 3.1.5 Based on the American Joint Committee on Cancer (AJCC), 6<sup>th</sup> edition (Appendix III): stage of transitional cell carcinoma (TCC) must be stages T2-T4a; Nx, N0 or N1; and M0; **OR** patients with primary bladder TCC grade 3/3 with AJCC clinical stage T1 who are felt to require definitive local therapy. Patients who have involvement of the prostatic urethra with TCC that was visibly completely resected, and have no evidence of stromal invasion of the prostate, remain eligible. They may not have evidence of distant metastases as determined by the following staging studies:
- 3.1.5.1 Chest x-ray (or chest CT scan) within 8 weeks prior to registration
- 3.1.5.2 Abdominal/pelvic CT scan within 8 weeks prior to registration
- 3.1.6 History and physical examination including vital signs and body surface area within 4 weeks prior to registration
- 3.1.7 Zubrod performance status of  $\leq 2$  (Appendix II)
- 3.1.8 Age  $\geq 18$
- 3.1.9 CBC/differential  $\leq 2$  weeks prior to registration, with adequate bone marrow function defined as follows:
- 3.1.9.1 Absolute neutrophil count (ANC)  $\geq 1,800$  cells/mm<sup>3</sup>
- 3.1.9.2 Platelets  $\geq 100,000$  cells/mm<sup>3</sup>
- 3.1.9.3 Hemoglobin  $\geq 8.0$  g/dl (Note: The use of transfusion or other intervention to achieve Hgb  $\geq 8.0$  g/dl is acceptable)
- 3.1.10 Adequate renal function, with serum creatinine  $\leq 3.0$  mg/dl
- 3.1.11 Adequate liver function, with serum bilirubin  $< 2.0$  mg/dl and SGOT/SGPT  $< 2.5$  x the upper normal limit
- 3.1.12 EKG and either MUGA scan or echocardiogram within 8 weeks prior to study entry
- 3.1.13 Adequate left ventricular ejection fraction (EF) by either MUGA scan or echocardiogram, with minimum EF of 40%.
- 3.1.14 Patients must be considered able to tolerate systemic chemotherapy combined with pelvic radiation therapy by the joint agreement of the participating radiation oncologist and medical oncologist
- 3.1.15 (8/12/09) Protocol treatment should begin within 3 to 12 weeks of the most recent TURB.
- 3.1.16 Patient must sign a study-specific informed consent prior to study entry
- 3.1.17 Negative pregnancy test for female patients of childbearing potential within 2 weeks prior to study entry
- 3.1.18 Women of childbearing potential and male participants must practice adequate contraception

#### **3.2 Conditions for Patient Ineligibility**

- 3.2.1 Prior invasive malignancy (except non-melanoma skin cancer) unless disease free for a minimum of 3 years.
- 3.2.2 Previous systemic chemotherapy with anthracyclines or taxanes, or prior systemic chemotherapy of any sort for TCC.
- 3.2.3 Previous pelvic radiation therapy.
- 3.2.4 Severe, active comorbidity defined as follows:
- 3.2.4.1 Unstable angina and/or congestive heart failure requiring hospitalization within the past 6 months
- 3.2.4.2 Transmural myocardial infarction within the past 6 months
- 3.2.4.3 Any history of inflammatory bowel disease
- 3.2.4.4 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

- 3.2.4.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.
- 3.2.4.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved may be immunosuppressive.
- 3.2.5 Pregnant or nursing women; this exclusion is necessary because treatment involves unforeseeable risks to the participant and to the embryo or fetus.
- 3.2.6 Men or women of childbearing potential who are sexually active and are not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
- 3.2.7 Prior allergic reaction to the study drug(s) involved in this protocol.
- 3.2.8 No block submitted for her2/neu analysis.

#### **4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT**

(In addition to the mandatory pre-testing for eligibility in Section 3.0)

**Note: The evaluations/interventions listed below should be done prior to the patient starting any protocol treatment (but may be done subsequent to the patient enrollment). In the unlikely event that results of any of these tests raise questions about the patient's eligibility for this study, please contact RTOG HQ immediately (215) 574-3189.**

##### **4.1 Additional Mandatory Pre-treatment Evaluations/Interventions (2/24/09)**

- See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.
- 4.1.1 Assessment of her2/neu overexpression in tumor tissue by immunohistochemistry **performed at the EM Laboratory at the Intermountain Central Laboratory in Utah** (See Section 10.2).
- 4.1.2 Laboratory studies within 4 weeks prior to study entry, including routine electrolytes and BUN/creatinine, alkaline phosphatase, SGOT/SGPT, bilirubin, magnesium and calcium
- 4.1.3 Cystoscopic evaluation by a participating urologic surgeon will include as thorough as possible a TURB, bimanual examination under anesthesia, four quadrant bladder and prostatic urethra mucosal biopsies as well as a biopsy of the base of the resected tumor site. Those patients referred from outside will be re-resected by the participating urologist.
- 4.1.4 Urine cytology.

#### **5.0 REGISTRATION AND TREATMENT ASSIGNMENT PROCEDURES**

##### **5.1 Summary of Procedures (02/24/09)**

This study incorporates a two-step registration process.

**Step 1** of registration entails web registration as detailed in Section 5.2.

- Institutions will then have 3 weeks to submit the tissue assay to the **RTOG Biospecimen Resource** for her2/neu analysis, as detailed in Section 10.2.
- The **Intermountain Central Laboratory** will fax results of the her2/neu analysis to institutions within 1-2 business days.

**Step 2** of registration entails web registration and entering the her2/neu results into the second step eligibility checklist.

- A treatment assignment (either paclitaxel or paclitaxel plus trastuzumab) will then be provided along with a new data submission calendar.

**(8/12/09)** Please remember that protocol treatment should begin within 3 to 12 weeks following the most recent TURB.

##### **5.2 Regulatory Pre-Registration Requirements (8/12/09)**

- 5.2.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification

Form, [http://www.rtog.org/pdf\\_file2.html?pdf\\_document=CTSUIRB CertifForm.pdf](http://www.rtog.org/pdf_file2.html?pdf_document=CTSUIRB CertifForm.pdf), prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions\*)  
\*Note: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

#### **5.2.2** Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

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

#### **5.2.3** Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

##### **5.2.3.1** For institutions that do not have an approved LOI for this protocol:

International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See [http://www.rtog.org/pdf\\_forms.html?members/forms=Intl\\_LOI\\_Form.doc](http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc)

##### **5.2.3.2** For institutions that have an approved LOI for this protocol:

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

### **5.3** General Web Registration Instructions

Patients can be registered only after eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>).
- The institution must complete the Password Authorization Form at [www.rtog.org/members/webreg.html](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site ([www.rtog.org](http://www.rtog.org)), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET.

## **6.0 RADIATION THERAPY [Note: Intensity Modulated Radiation Therapy (IMRT) Is Not Allowed on This Study]**

### **6.1 Dose Specifications (02/24/09) (8/12/09)**

All patients will receive 7.1 weeks of radiotherapy 5 days per week concurrently with paclitaxel. Patients with her2/neu overexpression will also receive trastuzumab. Radiotherapy will be started within 3 to 12 weeks of maximal TURB on a Monday, Tuesday, or Wednesday. Radiotherapy will be continuous, *without* a planned break for tumor assessment during treatment, as has been done in prior bladder preservation protocols of patients considered to be cystectomy candidates. The overall schema is for small pelvic treatment for 22 fractions at 1.8 Gy per daily fraction (5 days per week) to 39.6 Gy, followed by a reduction to the whole bladder using the same fractionation for 8 fractions to 54 Gy, and finally a reduction to the bulky tumor area with margin (partial sparing of the bladder) for an additional 6 fractions at 1.8 Gy to a total dose 64.8 Gy.

Note: For any questions regarding the radiation fields, please contact the Radiation Oncology study section chair, Dr. Pollack, at 305-243-4916.

### **6.2 Technical Factors**

Treatment should begin with a high-energy linear accelerator with 10 MV photons or greater using a four-field box for the initial small pelvic field. Alternative field arrangements may be used for the remainder of the treatment, although typically a four-field box is utilized throughout.

### **6.3 Localization, Simulation, and Immobilization (8/12/09)**

Conformal radiotherapy will be used. Patients will be positioned supine. A pelvic immobilization device such as an alpha cradle or vacuum bag is recommended. A planning CT scan of the pelvis will be obtained. The patient must void to empty the bladder immediately prior to simulation. Although contrast may be used, contrast in the bladder and rectum is not necessary for CT simulation and is not recommended; the insertion of contrast tends to distort the bladder and rectal volume and shape. The rectum should be as empty as possible for simulation; an enema may be given to accomplish this. The rectum under these conditions is more representative of rectal volume during treatment.

### **6.4 Treatment Planning/Target Volumes: CT-based planning must be used**

**6.4.1 (11/7/06) *Small Pelvic Fields (Appendix IV)*** Four fields must be used to encompass the entire bladder, prostate, and pelvic lymph nodes below the common iliac bifurcation. The CTV1 field margins in the superior-inferior dimensions should extend from mid-sacro-iliac region to just below the obturator foramen. The anterior-posterior opposed fields should extend 1.5-2.0 cm laterally beyond the medial aspect of the pelvic bones to encompass the iliac lymph nodes. Customized blocks should be used on the inferior lateral edges of these fields to reduce exposure of the femoral heads. The parallel-opposed lateral fields will extend at least 2.5 cm anteriorly of the bladder boundary, as defined on CT, although care should be taken to avoid fall-off anteriorly and < 2.5 cm may be required in some patients. The posterior margin should also be 2.5 cm beyond the bladder or any visible tumor mass. Inferiorly on the lateral fields, corner blocks should be used to shield the soft tissue inferior to the pubic symphysis anteriorly and the anal canal posteriorly. Superiorly on the lateral fields, a corner block should be placed anteriorly to shield bowel anterior to the external iliac lymph nodal chain. The fields should be adjusted to cover unusual anatomical variations, such as a bladder diverticulum, cytocele, or herniation into the anterior abdominal wall.

**6.4.2 *Whole Bladder Field:*** The Whole Bladder (CTV2) encompasses the entire bladder plus any bladder-associated masses visible on CT or other imaging modality (e.g., MRI, PET). The CTV2 may be treated with either a block margin of 2.5 cm, with the dose prescribed to the minimum isodose surface encompassing the CTV2 or a PTV = CTV2 + 2 cm may be created and treated so that the minimum dose to the PTV is no less than 95% of the isocentric dose.

**6.4.3 *Tumor Boost Field:*** The Tumor Boost (CTV3) encompasses the GTV, which includes any bladder-associated masses defined by CT or other imaging modality (e.g., MRI, PET) and cystoscopy. The treating radiation oncologist should consult the urologist who performed the TURB and the resulting cystoscopy report to determine the area of the original tumor as seen during exam under anesthesia and TURB. The Tumor Boost GTV may be treated with either a block margin of 2.5 cm, with the dose prescribed to the minimum isodose surface encompassing the CTV3 or a PTV = CTV3 + 2 cm may be created and treated so that the minimum dose to the PTV is no less than 95% of the isocentric dose.

### **6.5 Critical Structures**

The dose will be specified to the minimum isodose surface that surrounds the PTV. The minimum dose within the PTV will be no less than 95% of the isocentric dose. The maximum dose will not exceed 107% of the prescription dose. The dose to the femoral heads should be less than 50 Gy.

The rectosigmoid volume (entire contents) from the ischial tuberosities to above the sigmoid flexure (above the bladder) should be outlined and the 55 Gy line should not encompass the full-width of the rectosigmoid. A DVH for the rectum and bladder (minus the GTV) must be submitted.

#### **6.6 Documentation Requirements**

The CT plan must be submitted to RTOG Headquarters within 7 working days of initiation of treatment. The initial approved small pelvis port films must be submitted within 7 working days of treatment start. Digitally reconstructed radiographs of the treatment fields must be submitted within 7 working days of treatment start. Weekly ports are required for all fields (e.g., AP or PA, left or right lateral, one of two opposed obliques). Other forms of target localization may be used to supplement weekly port films, such as ultrasounds, CT, or cone beam CT imaging. However, RTOG Headquarters submission requirements are for one set of approved port films taken at the beginning of treatment and at any field change.

#### **6.7 Treatment Interruption**

If a grade 3 hematologic toxicity (ANC, platelets) develops during chemoradiotherapy, all treatment should be discontinued for a minimum of one week. Treatment may be resumed when the hematologic toxicity resolves to < grade 2. If these laboratory values have not been reached after a one week delay, they should be checked weekly until they become acceptable. If after 3 weeks the blood counts have not recovered, all protocol treatment should be discontinued and the patients should be treated on an individual basis.

For a grade 3 acute colitis, cystitis or any other grade 3 infield (radiation-related) toxicity during any treatment week, treatment should be delayed until the toxicity subsides to the grade 2 level. The treatment should be restarted with a 25% reduction in paclitaxel. If the delay is greater than 3 weeks, then the patient should be considered intolerant of protocol therapy and appropriate off-protocol therapy given.

#### **6.8 Compliance Criteria**

In keeping with the recommendations of the RTOG Quality Control Committee, compliance will be scored in relation to field borders, radiation dose, fractionation, and elapsed days. Each parameter will be scored as being per protocol, a variation (acceptable), or a deviation (unacceptable). Plans illustrating the isodose distributions through the central plane of each site should be submitted to RTOG Headquarters. The DVH for the rectosigmoid should be submitted.

#### **6.9 R.T. Quality Assurance Reviews**

The Radiation Oncology Co-Chair, Alan Pollack, MD, will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Pollack will perform the next review after complete data for the next 20 cases enrolled have been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first. These reviews will be ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

#### **6.10 Radiation Toxicity (8/12/09)**

Potential toxicities associated with radiation therapy to the pelvis include loss of pubic hair, cutaneous erythema in the treated area, increased urinary frequency (which could be permanent), fatigue, nausea, vomiting, rectal irritation, dyspareunia, ovarian failure in women, and sterility. Less likely but potentially serious toxicities include weight loss, rectal ulcers, hematochezia, bowel obstruction, bowel perforation, ureteral obstruction, and fistula formation. Bleeding from the bladder mucosal surface is potentially both an acute and chronic complication.

#### **6.11 (8/12/09) Radiation Therapy Adverse Event Reporting**

See Sections 7.8-7.9.

### **7.0 DRUG THERAPY**

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

**Note that patients with her2/neu overexpression will receive paclitaxel and trastuzumab as described below. Patients without her2/neu overexpression will receive paclitaxel in an identical fashion but will have trastuzumab omitted from their therapy.**

**Patient grouping based on her2/neu status is as follows:**

- **Her2/neu 2+ or 3+ staining: Group 1 (includes trastuzumab)**
- **Her2/neu 0 or 1+ staining: Group 2 (no trastuzumab)**

## SCHEMA

|  |                                  |  |
|--|----------------------------------|--|
| <b>R<br/>E<br/>G<br/>I<br/>S<br/>T<br/>E<br/>R</b> | <b>A<br/>S<br/>S<br/>A<br/>Y</b> | <p><b>Group 1: Patients with her2/neu overexpression</b><br/> <i>Radiation Therapy</i><br/>                     1.8 Gy qd for 5 fx/wk, for a total of 36 fx (1.8 Gy small pelvic fields x 22 fx, then reduction for 1.8 Gy x 8 fx, then 1.8 Gy boost x 6 fx for a total dose of 64.8 Gy)</p> <p><i>Chemotherapy</i><br/>                     Paclitaxel 50 mg/m<sup>2</sup>: d 1, 8, 15, 22, 29, 36, 43<br/>                     Trastuzumab 4 mg/kg: d 1<br/>                     Trastuzumab 2 mg/kg: d 8, 15, 22, 29, 36, 43</p> <hr/> <p><b>Group 2: Patients without her2/neu overexpression</b><br/> <i>Radiation Therapy</i><br/>                     1.8 Gy qd for 5 fx/wk, for a total of 36 fx (1.8 Gy small pelvic fields x 22 fx, then reduction for 1.8 Gy x 8 fx, then 1.8 Gy boost x 6 fx for a total dose of 64.8 Gy)</p> <p><i>Chemotherapy</i><br/>                     Paclitaxel 50 mg/m<sup>2</sup>: d 1, 8, 15, 22, 29, 36, 43</p> |
|--|----------------------------------|--|

Note:

Radiation may be started on Monday, Tuesday, or Wednesday.

Chemotherapy may be started on Monday, Tuesday, or Wednesday and should be given on the same day (± 1 day) each week. Regardless of the day of the week, the starting date of paclitaxel ± trastuzumab should correspond to the first day of radiation therapy.

**7.1 Chemoradiotherapy**

7.1.1 Body surface area calculations will be based on actual body weight. The following premedication for paclitaxel is recommended:

| Agent                | Dose   | Route       | Administration Time                  |
|----------------------|--------|-------------|--------------------------------------|
| Dexamethasone        | 20 mg  | Oral        | 12 and 6 hours prior to paclitaxel   |
| Dexamethasone        | 20 mg  | Intravenous | 30 to 60 minutes prior to paclitaxel |
| Diphenhydramine      | 50 mg  | Intravenous | 30 to 60 minutes prior to paclitaxel |
| Cimetidine <u>or</u> | 300 mg | Intravenous | 30 to 60 minutes prior to paclitaxel |
| Ranitidine           | 50 mg  | Intravenous | 30 to 60 minutes prior to paclitaxel |

**7.1.2 Chemotherapy (8/12/09)**

7.1.2.1 **Patients without her2/neu overexpression:** Paclitaxel plus irradiation will begin within 3 to 12 weeks following the most recent TURB.

7.1.2.2 **Patients with her2/neu overexpression:** Paclitaxel and trastuzumab plus irradiation will begin within 3 to 12 weeks following the most recent TURB. Paclitaxel and trastuzumab should always be administered on the same day.

7.1.3 Paclitaxel (50 mg/m<sup>2</sup>) is to be administered as a 1-hour infusion on days 1, 8, 15, 22, 29, 36, and 43. The recommended post-paclitaxel i.v. hydration is NS at a rate of 500 cc/hr for 1 hour. If necessary, drug may be administered one day earlier or later from the previous week.

7.1.4 Trastuzumab at 4 mg/kg is to be administered as an intravenous infusion over 90 minutes on day 1 only.

7.1.5 Trastuzumab at 2 mg/kg is to be administered as an intravenous infusion over 30 minutes on days 8, 15, 22, 29, 36, and 43. If necessary, trastuzumab may be administered one day earlier or later in a given week, and always on the same day as paclitaxel.

7.1.6 Radiation will be administered per Section 6.1. On days when chemotherapy is also given, the radiation may be prior to or following chemotherapy administration.

7.1.7 Standard antiemetic regimens will not be required, but may be used if necessary.

7.1.8 In week 11 or 12 (4-5 weeks following completion of chemoradiotherapy), the patient will have an evaluation of response as described in Section 8.2.

**7.2 Paclitaxel (Taxol®) (9/7/05)**

7.2.1 **Formulation:** Paclitaxel<sup>37-41</sup> is a poorly soluble plant product from the western yew, *Taxus brevifolia*. Improved solubility requires a mixed solvent system with further dilutions of either

0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

**7.2.2** Preparation: A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel for injection must be diluted before administration with 5% dextrose USP, 0.9% sodium chloride USP, or 5% dextrose in Ringer's injection to a final concentration of 0.3 to 1.2 milligrams/milliliter. This solution is stable for 27 hours under ambient temperature (25 degrees Celsius) and room lighting (Prod Info Taxol®, 1997). Use 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution have been observed after preparation of paclitaxel (NOTE: acceptable limits established by the USP Particular Matter Test for LVPs). Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g., Millex-GV Millipore Products) into the i.v. fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

**7.2.3** Administration: Paclitaxel, at the appropriate dose and dilution, will be given as a one-hour infusion. The paclitaxel is mixed in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI i.v. administration with 0.22 micron in-line filter. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the i.v. administration sets (polyethylene or polyolefin) which are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

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

**7.2.5** Adverse Effects: See Package Insert for complete listing.

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

**7.2.6** Supply: Commercially available.

### **7.3 Trastuzumab (NSC# 688097)**

**7.3.1** Dose Formulation and Preparation: Trastuzumab is supplied as a freeze-dried preparation at a nominal content of 440 mg per vial for parenteral administration. The study drug is formulated in histidine, trehalose, and polysorbate 20. Each vial is reconstituted with 20 mL of Bacteriostatic Water for Injection (BWI), USP (containing 1.1% benzyl alcohol), which is supplied with each vial. The reconstituted solution contains 21 mg/mL trastuzumab and will be added to 250 mL of 0.9% Sodium Chloride Injection, USP. This formulation is designed for multiple uses and must be used within 28 days of reconstitution. Reconstituted trastuzumab should appear clear to slightly opalescent and colorless to pale yellow.

**7.3.2** Administration: Patients with her2/neu overexpression will receive trastuzumab administered intravenously 4 mg/kg loading dose over 90 minutes on day 1, followed by 2 mg/kg weekly beginning day 8. Dextrose should not be used. For patients with known sensitivity to benzyl alcohol, use sterile water for infusion to reconstitute the trastuzumab and use the resulting product immediately. The initial dose will be administered over 90 minutes, and if well tolerated, subsequent infusion periods may be shortened to 30 minutes. If the initial or subsequent doses are not well tolerated (e.g., the patient experiences infusion-related fever or chills), subsequent infusions may be shortened only after a dose is well tolerated. Patients must remain under

medical supervision for 60 minutes following completion of the initial dose. If no adverse events occur, the post-infusion observation period for the second infusion may be shortened to 30 minutes, and eliminated entirely with subsequent infusions.

**7.3.3** Storage: Vials of the lyophilized formulation of trastuzumab must be placed in a refrigerator (2-8 degrees Celsius) upon receipt to ensure physical and biochemical integrity. DO NOT FREEZE. Trastuzumab may be sensitive to shear-induced stress. DO NOT SHAKE. Vigorous handling of solutions of trastuzumab may result in aggregation of the protein and may create cloudy solutions. The reconstituted formulation (400 mg vial) is designed for multiple use. Unused drug may be stored for up to 28 days under refrigeration. Reconstituted trastuzumab should appear clear to slightly opalescent and colorless to pale yellow.

**7.3.4** Adverse Effects  
There have been rare reports of severe pulmonary reactions leading to death associated with trastuzumab treatment. Such reactions may include bronchospasm, hypoxia, pulmonary infiltrate, adult respiratory distress syndrome (ARDS), pneumonitis/fibrosis, non-cardiogenic pulmonary edema, and pleural effusion. These reactions may or may not occur as sequelae of infusion reactions. Symptomatic lung disease at baseline or extensive pulmonary metastases increase the risk for development of a severe pulmonary reaction, although rare incidents of pneumonitis and ARDS with fatal outcome have also been reported in patients without history of pulmonary disease or metastasis.

The Comprehensive Adverse Events and Potential Risks List (CAEPR) for Trastuzumab are listed in the table below.

**Comprehensive Adverse Events and Potential Risks List (CAEPR)  
for Trastuzumab (NSC #688097)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' <http://ctep.cancer.gov/reporting/adeers.html> for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for trastuzumab.

Version 1.0, February 25, 2005 <sup>1</sup>

| Category (Body System)    | Adverse Events with Possible Relationship to Trastuzumab (CTCAE v3.0 Term) | 'Agent Specific Adverse Event List' (ASAEL)  |
|---------------------------|--|--|
| <b>ALLERGY/IMMUNOLOGY</b> |  |  |
|                           | Allergic reaction/hypersensitivity (including drug fever)                  | <b><i>Allergic reaction/hypersensitivity (including drug fever)</i></b>                |
|                           | Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)   | <b><i>Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)</i></b> |
|                           | Allergy/Immunology - Other (Angioedema)                                    |  |
| <b>BLOOD/BONE MARROW</b>  |  |  |
|                           | Hemoglobin   | <b><i>Hemoglobin</i></b>   |
|                           | Leukocytes (total WBC)   |  |
|                           | <sup>2</sup> Neutrophils/granulocytes (ANC/AGC)                            | <b><i>Neutrophils/granulocytes (ANC/AGC)</i></b>                                       |
| <b>CARDIAC ARRHYTHMIA</b> |  |  |
|                           | Sinus tachycardia  | <b><i>Sinus tachycardia</i></b>  |
|                           | Supraventricular arrhythmia - nodal/junctional                             |  |
| <b>CARDIAC GENERAL</b>    |  |  |
|                           | Cardiac General - Other (Cardiac arrest)                                   |  |
|                           | Cardiac General - Other (Cardiomyopathy)                                   |  |
|                           | Cardiac troponin I (cTnI)  |  |
|                           | <sup>3</sup> Hypertension  |  |
|                           | Hypotension  |  |
|                           | Left ventricular systolic dysfunction                                      | <b><i>Left ventricular systolic dysfunction</i></b>                                    |
|                           | Pericardial effusion (non-malignant)                                       |  |

|                                    |   |  |
|------------------------------------|---|--|
|                                    | Pericarditis  |  |
| <b>CONSTITUTIONAL SYMPTOMS</b>     |   |  |
|                                    | Fatigue (asthenia, lethargy, malaise)   | <b>Fatigue (asthenia, lethargy, malaise)</b>   |
|                                    | Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)  | <b>Fever (in the absence of neutropenia, where neutropenia is defined as ANC &lt;1.0 x 10e9/L)</b> |
|                                    | Rigors/chills   | <b>Rigors/chills</b>   |
| <b>DERMATOLOGY/SKIN</b>            |   |  |
|                                    | Rash/desquamation   | <b>Rash/desquamation</b>   |
|                                    | Rash: acne/acneiform  |  |
|                                    | Ulceration  |  |
|                                    | Urticaria (hives, welts, wheals)  |  |
| <b>GASTROINTESTINAL</b>            |   |  |
|                                    | Anorexia  | <b>Anorexia</b>  |
|                                    | Diarrhea  | <b>Diarrhea</b>  |
|                                    | Mucositis/stomatitis (functional/symptomatic) – Select  | <b>Mucositis/stomatitis (functional/symptomatic) - Select</b>                                      |
|                                    | Nausea  | <b>Nausea</b>  |
|                                    | Vomiting  | <b>Vomiting</b>  |
| <b>INFECTION</b>                   |   |  |
|                                    | Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C) |  |
|                                    | Infection - Other (Herpes simplex)  |  |
|                                    | Infection with unknown ANC - Select   | <b>Infection with unknown ANC - Select</b>   |
| <b>METABOLIC/LABORATORY</b>        |   |  |
|                                    | Alkaline phosphatase  | <b>Alkaline phosphatase</b>  |
|                                    | AST, SGOT (serum glutamic oxaloacetic transaminase)   | <b>AST, SGOT (serum glutamic oxaloacetic transaminase)</b>   |
|                                    | GGT (gamma-glutamyl transpeptidase)   | <b>GGT (gamma-glutamyl transpeptidase)</b>   |
| <b>PAIN</b>                        |   |  |
|                                    | Pain - abdomen NOS  | <b>Pain - abdomen NOS</b>  |
|                                    | Pain - back   |  |
|                                    | Pain - bone   |  |
|                                    | Pain - chest/thorax NOS   | <b>Pain - chest/thorax NOS</b>   |
|                                    | Pain - head/headache  | <b>Pain - head/headache</b>  |
|                                    | Pain - joint  | <b>Pain - joint</b>  |
|                                    | Pain - muscle   | <b>Pain - muscle</b>   |
|                                    | Pain - neuralgia/peripheral nerve   |  |
|                                    | Pain - tumor pain   | <b>Pain - tumor pain</b>   |
|                                    | Pain NOS  |  |
| <b>PULMONARY/UPPER RESPIRATORY</b> |   |  |
|                                    | Adult respiratory distress syndrome (ARDS)  |  |
|                                    | Bronchospasm, wheezing  | <b>Bronchospasm, wheezing</b>  |
|                                    | Cough   | <b>Cough</b>   |
|                                    | Dyspnea (shortness of breath)   | <b>Dyspnea (shortness of breath)</b>   |
|                                    | Hypoxia   | <b>Hypoxia</b>   |
|                                    | Pleural effusion (non-malignant)  |  |
|                                    | Pneumonitis/pulmonary infiltrates   |  |
|                                    | Pulmonary - Other (Non-cardiogenic pulmonary edema)   |  |
|                                    | Pulmonary fibrosis  |  |
|                                    | Voice changes   |  |
| <b>SYNDROMES</b>                   |   |  |
|                                    | Cytokine release syndrome/acute infusion reaction   |  |
|                                    | Flu-like syndrome   |  |

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [ADEERSMD@tech-res.com](mailto:ADEERSMD@tech-res.com). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup>Fatal event when given in combination with Xeloda and Taxotere.

<sup>3</sup>Associated with infusion.

**Also reported on trastuzumab trials but with the relationship to trastuzumab still undetermined:**

Auditory/Ear – hearing loss (without monitoring program)

Cardiac arrhythmia – sinus bradycardia

Death – sudden death

Endocrine – hypothyroidism

Gastrointestinal – colitis; enteritis; esophageal ulcer; GI obstruction; ileus

Growth and development – reduced growth velocity

Hemorrhage/Bleeding – hemorrhage; upper GI hemorrhage; urinary hemorrhage

Hepatobiliary/Pancreas – pancreatitis

Infection – viral hepatitis

Metabolism/Laboratory – hyperbilirubinemia; hypercalcemia; hypoglycemia; hypomagnesemia; hyponatremia

Musculoskeletal/Soft Tissue – muscle weakness; myopathy; osteonecrosis

Neurology – anxiety; apnea; ataxia; CNS ischemia; confusion; depression; dizziness; hydrocephalus; meningitis; mental status; psychosis; seizure; sensory neuropathy; somnolence/depressed level of consciousness; syncope

Ocular/Visual – blurred vision

Pulmonary/Upper Respiratory – laryngeal edema; pneumothorax

Renal/Genitourinary – GU obstruction; renal failure

Syndromes – nephrotic syndrome

Vascular – thrombosis/thrombus/embolism

**Notes:** Trastuzumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

**7.3.5** *Accountability and Supply*

The Principal Investigator (or authorized designee listed by the Investigator on the site's most recent Supplemental Investigator Data Form [IDF] on file with the PMB) at each participating institution may request trastuzumab from NCI's Pharmaceutical Management Branch (PMB). The updated version (11/10/03) of each institution's Drug Authorization Review and Tracking System (DARTS) will require selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the Investigator during the annual Investigator registration process. This process must be completed before a drug order can be entered for that investigator. Any changes to this information will require updating the first two pages of the IDF, having the Investigator sign the revised IDF, and returning it to the PMB via fax at 301-402-4870. Questions about the process should be directed to the PMB at 301-496-5725 Monday through Friday from 8:30 – 4:30 Eastern Time. PMB policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions unless prior approval from PMB is obtained. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN, Room 7149, Bethesda, MD 20892.] All forms can be accessed on the NCI web site, <http://ctep.cancer.gov/forms/index.html>. The Investigator Brochure (IB), if available, for this drug will be supplied by the PMB/NCI. All requests for IBs should be e-mailed to [ibcoordinator@mail.nih.gov](mailto:ibcoordinator@mail.nih.gov) or the IB Coordinator may be contacted at 301-496-5725.

**7.3.6** *Clinical Trials Agreement*

The agent supplied by CTEP, DCTD, NCI used in this protocol—**trastuzumab (Herceptin<sup>®</sup>) [hereinafter referred to as “Agent”]**—is provided to the NCI under a Collaborative Research and Development Agreement (CRADA) between **Genentech, Inc. [hereinafter referred to as “Collaborator”]** and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator contained within the terms of award, apply to the use of the Agent in this study:

Agent may not be used for any purpose outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for

Agent are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.

Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

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

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

**Regulatory Affairs Branch, CTEP, DCTD, NCI**  
**Executive Plaza North, Suite 7111**  
**Bethesda, Maryland 20892**  
**FAX (301) 402-1584**  
**Email: [anshers@ctep.nci.nih.gov](mailto:anshers@ctep.nci.nih.gov)**

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

#### **7.4 Dose Modifications for Paclitaxel**

**All dose modifications will be based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.**

Lab assessments will be repeated weekly during treatment and dose modification will be made according to the guidelines below at each time point (Days 1, 8, 15, 22, 29, 36, 43). Once dose reduction has occurred, future doses may not be increased. If drug is withheld, reassessment should occur weekly until toxicity has resolved. If delay of greater than 21 days is required, additional drug should not be administered and the patient should be removed from all protocol treatment.

For patients with her2/neu overexpression, continue treatment with trastuzumab if paclitaxel is withheld.

##### **7.4.1. Hematologic Toxicity (ANC, Platelets)**

Granulocytopenia alone will not be considered the only criteria for dose reduction. For patients with grade 4 neutropenia, paclitaxel should be discontinued permanently. For patients with grade 3 neutropenia ( $< 1000$  cells/mm<sup>3</sup>) and/or grade 3 thrombocytopenia ( $< 50,000$  cells/mm<sup>3</sup>), chemoradiotherapy will be stopped for a minimum of one week and the CBC with differential will be repeated weekly. Treatment may be resumed once hematologic toxicity recovers to  $<$  grade 2. Upon resumption, the paclitaxel dose for hematologic toxicity will be modified as follows:

**% Calculated Dose**

|                           |       | Platelet Count                |                               |                               |                               |
|---------------------------|-------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
|                           |       | > 150K                        | 100-149K                      | 75-99K                        | < 75K                         |
| <b>Nadir ANC (x 1000)</b> | ≥ 1.0 | 100                           | 100                           | 100                           | 50                            |
|                           | < 1.0 | 50                            | 50                            | 50                            | 50                            |
|                           | < 0.5 | <b>Discontinue paclitaxel</b> | <b>Discontinue paclitaxel</b> | <b>Discontinue paclitaxel</b> | <b>Discontinue paclitaxel</b> |

**7.4.2** Hepatic

Grade 3-4 elevation of SGOT, SGPT, or bilirubin due to paclitaxel will require withholding dose, followed by a dose reduction of 25% after recovery to ≤ grade 2. A second dose reduction will not be allowed for continued toxicity.

**7.4.3** Renal

Grade 3-4 elevation of serum creatinine due to paclitaxel will require one dose reduction of 25% after recovery to ≤ grade 2. A second dose reduction will not be allowed for continued toxicity.

**7.4.4** Mucositis

Grade 2 or greater will require withholding dose, followed by a dose reduction of 25% after recovery to ≤ grade 1. Recurrence after one dose reduction will require that the patient receive no further paclitaxel.

**7.4.5** Gastrointestinal Toxicity

If grade 3 or 4 nausea/vomiting or ileus toxicity occurs, in spite of administration of prophylactic antiemetic regimen, the subsequent cycle should be reduced by 25%. Toxicity must resolve before treatment is resumed. In the event of grade 3 or 4 nausea/vomiting or ileus toxicity in spite of the dose reduction, no further paclitaxel therapy should be given.

If grade 3 or greater diarrhea occurs in spite of administration of prophylactic antimotility agents, the dose of paclitaxel should be reduced by 25%. Toxicity must resolve to grade 1 or less before treatment is resumed. In the event of grade 3 or 4 diarrhea in spite of the dose reduction, no further paclitaxel therapy should be given.

**7.4.6** Neurologic Toxicity

In the event of grade 4 neurologic toxicity, paclitaxel will be discontinued. A dose reduction of 25% in paclitaxel will be required in the event of grade 3 neurotoxicity (neurosensory, neuromotor). If, in a subsequent cycle, despite the dose reduction, grade 3 neurotoxicity is observed, no further paclitaxel therapy should be given. Patients must return to a toxicity of grade 1 or less before retreatment.

**7.4.7** Hypersensitivity Reactions

An infusion will be discontinued if a patient develops any signs of severe hypersensitivity reaction (dyspnea, symptomatic hypotension, angioedema, generalized urticaria, or chest pain). Patients should be treated with the necessary support measures and removed from protocol therapy. The following management of hypersensitivity reactions is suggested:

- Administration of diphenhydramine 50 mg i.v. (or its equivalent);
- Administration of epinephrine (or its equivalent) every 15-20 minutes until the reaction subsides or a total of six doses are given;
- If hypotension is present that does not respond to epinephrine, administration of i.v. fluids is recommended;
- If wheezing is not responsive to epinephrine, administration of nebulized albuterol (or its equivalent) is recommended;
- Although corticosteroids have no effect in the initial reaction, they have been shown to block "late" allergic reactions (i.e., those that occur within a few hours). Thus, methylprednisolone 125 mg i.v. (or its equivalent) may be given to prevent recurrent or ongoing allergic manifestations.

In the event of grade  $\leq 2$  hypersensitivity reactions (flushing, skin rash), the infusion may be continued with further support as necessary (steroids, antihistamines, etc.). There will be no dose modifications for hypersensitivity reactions, but extreme caution with subsequent cycles should be employed.

#### 7.4.8 Cardiac Toxicity

There will be no dose modifications for asymptomatic (grade 1 or 2) cardiac toxicity or asymptomatic hypotension. In the event of first degree AV block, paclitaxel therapy will be continued at full dose under continuous cardiac monitoring. In the event of grade 3 or 4 cardiac toxicity, i.e., CHF, no further paclitaxel will be given.

#### 7.4.9 Myalgia/Arthralgia

Myalgia/arthralgia will be classified as mild (grade 1): muscle and joint aches; moderate (grade 2): decreased function, decreased ability to perform daily tasks, but still functioning; or severe (grade 3): unable to function, confined to bed. Treatment for myalgia and arthralgias may include nonsteroidal anti-inflammatory medication (Toradol<sup>®</sup>, ibuprofen, etc.). If there is still no relief, narcotic pain medications may be used. Grade 3 toxicity, reasonably attributable to paclitaxel, will require a dose reduction of 25% following resolution to grade  $\leq 1$ . No further dose reduction will be permitted, and no further paclitaxel will be given.

### **7.5 Dose Modification for Trastuzumab**

**All dose modifications will be based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.**

There is no dose or schedule adjustment for trastuzumab based on specific toxicity criteria, except cardiac toxicity. On days when patients are scheduled to receive treatment, they should receive trastuzumab even if paclitaxel is not being administered due to toxicity.

#### 7.5.1 Cardiac

In the event of grade 3 or 4 cardiac toxicity (symptomatic CHF), no further trastuzumab will be given. The diagnosis of CHF should be confirmed with either a MUGA scan or echocardiogram. In the event of grade 1 or 2 arrhythmia, treatment may be stopped or continued at the discretion of the treating physician. In the event of grade 3 or 4 arrhythmia, no further trastuzumab will be given.

#### 7.5.2 Infusional/Hypersensitivity

##### 7.5.2.1 Grade 1-2 infusional or allergic reactions without bronchospasm or dyspnea:

- The infusion must be stopped and the patient must be monitored.
- Diphenhydramine hydrochloride will be administered. If the toxicity resolves within 3 hours, the infusion rate should be resumed at a slower rate. Resumption of trastuzumab in the next cycle is allowed at a slower rate and under close supervision.

##### 7.5.2.2 Grade 2 infusional or allergic reactions with bronchospasm:

- Trastuzumab must be stopped.
- The patient must be managed symptomatically and carefully monitored for exacerbation of respiratory symptoms.

##### 7.5.2.3 Grade 3-4 infusional or allergic reactions:

- Trastuzumab must be stopped.

#### 7.5.3 Pulmonary

If a patient develops symptoms suggestive of interstitial pneumonitis, adult respiratory distress syndrome (ARDS), or non-cardiogenic pulmonary edema, trastuzumab must be delayed and a thorough evaluation must be performed. If pneumonitis/fibrosis or pulmonary infiltrate is confirmed (and the relationship to trastuzumab cannot be excluded), trastuzumab must be permanently discontinued.

### **7.6 Criteria for Removal From Protocol Treatment**

- Progression of disease
- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flow sheet, and follow AE reporting guidelines in Section 7.8.1.
- A delay in chemotherapy > 3 weeks
- Inability of patient to comply with study regulations
- Withdrawal of informed consent
- The patient may withdraw from receiving treatment at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing and follow the guidelines set forth in the RTOG procedure manual.

## **7.7 Modality Review**

The Medical Oncology Co-Chair, M. Dror Michaelson, MD, PhD, will perform a Chemotherapy Assurance Review of all patients in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: per protocol; variation, acceptable; deviation unacceptable; not evaluable for chemotherapy review; or incomplete chemotherapy. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

## **7.8 Adverse Events (8/12/09)**

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, MedDRA version 6.0 for grading of all treatment related adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). The CTEP home page also can be accessed from the RTOG web page at <http://www.rtog.org/regulatory/regs.html>. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the table below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/qadeers\\_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/qadeers_main$.startup)).

Serious adverse events (SAEs) as defined in the table below will be reported using AdEERS. Sites also can access the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>) for this information.

**In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF).** In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

### **7.8.1 Adverse Events (AEs)—RTOG AE PHONE: 215-717-2762 (available 24 hours/day) [8/12/09]**

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (e.g.: attribution of unrelated, unlikely, possible, probable or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. January 2005; <http://ctep.cancer.gov/reporting/adeers.html>.]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.X also must be reported via AdEERS.**

**NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.**

### **7.8.2 Serious Adverse Event (SAEs) Reporting (8/12/09) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.**

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

**Definition of an SAE:** Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

**All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.**

**SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.**

**7.8.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)**

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at <http://ctep.cancer.gov/forms/index.html>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

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

**7.9 AdEERS Expedited Reporting Requirements**

**(8/12/09)** CTEP defines expedited AE reporting requirements for phase 1 and 2 trials as described in the tables below. Important: All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

**Phase 1 Trials: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent**

|  | Grade 1                 | Grade 2          | Grade 2      | Grade 3                         |                          | Grade 3                       |                         | Grades 4 & 5 <sup>2</sup> |
|--|-------------------------|------------------|--------------|---------------------------------|--------------------------|-------------------------------|-------------------------|---------------------------|
|  | Unexpected and Expected | Unexpected       | Expected     | Unexpected with Hospitalization | without Hospitalization  | Expected with Hospitalization | without Hospitalization | Unexpected and Expected   |
| <b>Unrelated Unlikely</b>  | Not Required            | Not Required     | Not Required | 10 Calendar Days                | Not Required             | 10 Calendar Days              | Not Required            | 24-Hour; 5 Calendar Days  |
| <b>Possible Probable Definite</b>  | Not Required            | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days        | 24-Hour; 5 Calendar Days | 10 Calendar Days              | Not Required            | 24-Hour; 5 Calendar Days  |
| <sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:<br>AdEERS 24-hour notification followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> <li>• Grade 3 unexpected events with hospitalization or prolongation of hospitalization</li> <li>• Grade 4 unexpected events</li> <li>• Grade 5 expected events and unexpected events</li> </ul> <sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table. |                         |                  |              |                                 |                          |                               |                         |                           |
| March 2005   |                         |                  |              |                                 |                          |                               |                         |                           |

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

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

**Phase 2 Trials: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent**

|                                   | Grade 1                 | Grade 2          | Grade 2      | Grade 3                         |                                    | Grade 3                       |                                  | Grades 4 & 5 <sup>2</sup> | Grades 4 & 5 <sup>2</sup> |
|-----------------------------------|-------------------------|------------------|--------------|---------------------------------|------------------------------------|-------------------------------|----------------------------------|---------------------------|---------------------------|
|                                   | Unexpected and Expected | Unexpected       | Expected     | Unexpected with Hospitalization | Unexpected without Hospitalization | Expected with Hospitalization | Expected without Hospitalization | Unexpected                | Expected                  |
| <b>Unrelated Unlikely</b>         | Not Required            | Not Required     | Not Required | 10 Calendar Days                | Not Required                       | 10 Calendar Days              | Not Required                     | 10 Calendar Days          | 10 Calendar Days          |
| <b>Possible Probable Definite</b> | Not Required            | 10 Calendar Days | Not Required | 10 Calendar Days                | 10 Calendar Days                   | 10 Calendar Days              | Not Required                     | 24-Hour; 5 Calendar Days  | 10 Calendar Days          |

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:  
AdEERS 24-hour notification followed by complete report within 5 calendar days for:  

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:  

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

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

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

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

**7.10 CDUS Reporting**

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

**8.0 SURGERY**

**8.1 Pre-Chemoradiotherapy Evaluation:** Endoscopic evaluation should include:

- 8.1.1** Cystoscopy with tumor mapping by a participating urologist (See Section 4.1.3) on the initial Cystoscopic Report (See Appendix V);
- 8.1.2** (02/24/09) TURB of the tumor as thoroughly as is judged safely possible. Tumor specimens should be sent to the RTOG Biospecimen Resource as described in Section 10.0;
- 8.1.3** Tumor base and two biopsies at the periphery of the tumor by cold cup following TURB of the tumor for additional analysis of the completeness of the TURB;
- 8.1.4** Bimanual examination before and after TURB to evaluate possible residual tumor bulk;
- 8.1.5** Two mucosal biopsies from the bladder neck and prostatic urethra.

- 8.1.6 (02/24/09) An additional fresh biopsy specimen containing tumor should be placed in RNA/ater™ medium and stored in the refrigerator. These samples should be shipped to the RTOG Biospecimen Resource within 30 days (See Section 10.2.5 for full details).

**8.2 Post-Chemoradiotherapy Endoscopic Response Evaluation (8/12/09)**

This evaluation will take place 6-8 weeks following the completion of chemoradiotherapy. Evaluation will include: barbotage cytology, cystoscopy, tumor site transurethral biopsy, and bimanual examination after biopsy.

**8.3 Subsequent Endoscopic Evaluations**

While not required, we recommend subsequent cystoscopic evaluation every three months in the first year, every four months in the second year, every six months for three years, and then annually. Regular cystoscopic follow-up allows additional therapy, such as TURB or intravesical chemotherapy, to be initiated at the earliest prompt opportunity, if relapse occurs.

**9.0 OTHER THERAPY**

**9.1 Additional Treatment**

9.1.1 For patients who are treated with attempted bladder preservation, either TURB or intravesical drug therapy will be promptly considered for a local persistence or local re-occurrence if it occurs in patients without evidence of distant metastases. This subsequent therapy will be given at the discretion of the primary physicians. The rates of local recurrence and/or distant metastases will be reported.

9.1.2 For patients with persistence of muscle-invasive bladder cancer, or subsequent development of muscle-invasive bladder cancer, aggressive measures should be considered including surgical resection as tolerated and/or systemic chemotherapy.

9.1.3 For patients who develop distant metastases, additional therapies will be treated at the discretion of the primary physicians.

**9.2 Permitted Supportive Therapy**

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.2.1 **Antiemetics** may be used as necessary. Other than premedication for paclitaxel as recommended above in Section 7.0, no antiemetics are required.

9.2.2 **Anticoagulants** may be administered as required for other medical conditions. These should be adjusted according to standard medical practice around the time of cystoscopic surgery.

9.2.3 **Antidiarrheals** may be used as needed during and following chemoradiotherapy.

9.2.4 **Hematopoietic growth factors** should not be used prophylactically but may be added if necessary in individual patients.

**10.0 TISSUE/SPECIMEN SUBMISSION (02/24/09)**

**10.1 Rationale**

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high-quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for central review of pathology. Central review of tissue can be for eligibility and/or analysis.

(8/12/09) In this study, tissue will be submitted to the RTOG Biospecimen Resource for the purposes of her2/neu analysis. Remaining tissue, including tissue in paraffin block and fresh tissue obtained and stored in RNA/ater™, will be stored for tissue banking. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

**10.2 Specimen Collection for Her2/Neu Analysis and Tissue Banking**

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

10.2.1 At least one paraffin-embedded tissue block of the tumor must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.2 A Pathology Report documenting that the submitted block contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or

other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

- 10.2.3** A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource. The form must include the RTOG protocol number and patient's case number.
- 10.2.4** Slides created from block will be evaluated for her2 expression by immunochemistry using HercepTest. The interpretation of the slides will be done using image analysis on the ACIS system. Results of her2 testing will be available 1-2 business days after receipt of block from institutions, and results will be immediately provided to the submitting institution for patient grouping.
- 10.2.5** RNA/ater™ Sample  
At the time of initial TURB, a sample of fresh tissue should have been placed in RNA/ater™ solution and subsequently stored at 4C. RNA/ater™ is available from the Biospecimen Resource at the number listed below. (Institutions must have documentation of IRB approval before requesting the media.) RNA/ater™ 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. At a convenient time (within 30 days), refrigerated samples should be mailed via overnight mail to the address listed below. Samples can be safely sent at room temperature if received within 24 hours.
- 10.2.6** **(8/12/09)** Submit all tissue samples via overnight mail (to enable patient grouping) to:

**U.S. Postal Service Mailing Address: For Non-frozen Specimens Only**  
**RTOG Biospecimen Resource**  
**University of California San Francisco**  
**Campus Box 1800**  
**1657 Scott Street, Room 223**  
**San Francisco, CA 94143-1800**

**Courier Address (FedEx, UPS, etc.): For Frozen Specimens**  
**RTOG Biospecimen Resource**  
**University of California San Francisco**  
**1657 Scott Street, Room 223**  
**San Francisco, CA 94115**

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

### **10.3 Reimbursement**

RTOG will reimburse submitting institutions \$300 per case for fresh or flash frozen tissue or tissue in RNA/ater™ or \$200 per case for a block. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

### **10.4 Confidentiality/Storage**

(See the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/tissuebank/tissuefaq.html> for further details.)

- 10.4.1** Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.
- 10.4.2** Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

## 11.0 PATIENT ASSESSMENT

### 11.1 Study Parameters (11/7/06)

| Parameter   | Pre-Study      | During Chemo-Radiotherapy | At Post-Chemoradiotherapy Evaluation | Follow-Up Evaluation |
|---|----------------|---------------------------|--------------------------------------|----------------------|
| Body Surface Area                                     | X              |                           |                                      |                      |
| H&P   | X              | Weekly                    | X                                    | X                    |
| Weight  | X              | Weekly                    |                                      | X                    |
| Zubrod Status   | X              | X                         | X                                    | X                    |
| TURB  | X              |                           |                                      |                      |
| Cystoscopy  | X              |                           | X                                    | X <sup>a</sup>       |
| Urine Cytology  | X              |                           | X                                    | X <sup>a</sup>       |
| Bimanual Exam Under Anesthesia                        | X              |                           | X                                    | X <sup>a</sup>       |
| Bladder Biopsy  | X              |                           | X                                    |                      |
| CBC, Platelets, ANC, Diff                             | X <sup>e</sup> | Weekly                    | X                                    | X                    |
| Serum Creatinine, BUN                                 | X              | Weekly                    | X                                    | X                    |
| Bilirubin, SGOT, SGPT                                 | X              | X                         | X                                    |                      |
| Magnesium, Calcium, Routine Electrolytes <sup>g</sup> | X              |                           |                                      |                      |
| Alk Phos  | X              |                           |                                      |                      |
| Pregnancy Test <sup>d</sup>                           | X              |                           |                                      |                      |
| CT Scan of Ab, Pelvis                                 | X <sup>b</sup> |                           | X <sup>f</sup>                       | X <sup>f</sup>       |
| EKG   | X <sup>b</sup> |                           |                                      |                      |
| MUGA Scan or Echo                                     | X <sup>b</sup> |                           | X                                    | X <sup>h</sup>       |
| Chest X-ray/CT  | X <sup>b</sup> |                           | X <sup>f</sup>                       | X <sup>f</sup>       |
| Bone Scan   | X <sup>f</sup> |                           | X <sup>f</sup>                       | X <sup>f</sup>       |
| Tumor Tissue for Her2/neu Analysis                    | X              |                           |                                      |                      |
| Urodynamic Evaluation                                 |                |                           |                                      | X <sup>c</sup>       |

- a. Cystoscopy is recommended q3 months the first year after completion of treatment; q4 months the second year; q6 months x 3 years; then annually.
- b. No more than 8 weeks prior to treatment.
- c. In third post-treatment year for patients who still have native bladder. This will incorporate measures of average and peak urinary flow rate, bladder functional capacity, compliance, and leak pressures (continence).
- d. For women of childbearing potential, within 2 weeks prior to treatment.
- e. ≤ 2 weeks prior to registration.
- f. As indicated.
- g. Routine electrolytes include sodium, potassium, chloride, bicarbonate, and glucose.
- h. At year 1 and year 2 follow-up evaluations if MUGA scan was abnormal at the post-chemoradiotherapy evaluation. Frequency of MUGA scans in these instances is as deemed medically appropriate by the treating physicians but must be no less than twice per year until the abnormality resolves or is deemed irreversible.

## **11.2 Definition of Response**

The objective response of the local bladder tumor will be described as follows:

- **Complete Response (a CR or a pT0 response)** requires the absence of any tumor in the tumor-site biopsy specimen or elsewhere and a bimanual exam that does not indicate the presence of a tumor mass. For a primary tumor response, a urine cytology specimen that is not positive is also required.
- **Partial Response (PR)** requires that all response criteria of a CR except that the urine cytology remains positive or Cis is seen in the biopsy.
- **No Response (NR)** requires the continued presence of the tumor (T ≥ 1) in the tumor-site biopsy specimen, or elsewhere.
- **Progression** requires the increase of 50% or more in the largest diameter of the endoscopically appreciable tumor and the continued presence of tumor in the tumor-site biopsy specimen.

## **12.0 DATA COLLECTION**

Data should be submitted to:

**RTOG Headquarters  
1818 Market Street, Suite 1600  
Philadelphia, PA 19103**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

### **12.1 Summary of Data Submission (9/7/05)**

| <b><u>Item</u></b>                                     | <b><u>Due</u></b>  |
|--|--|
| Demographic Form <b>(A5)</b>                           | Within 2 weeks of study entry  |
| Initial Evaluation Form <b>(I1)</b>                    |  |
| Pathology Report <b>(P1)</b>                           |  |
| Slides/Blocks <b>(P2)</b>                              |  |
| Her2/neu Expression Report <b>(P6)</b>                 | Within 4 weeks of study entry  |
| <b><u>Preliminary Dosimetry Information:</u></b>       | Within 1 week of start of RT   |
| RT Prescription (Protocol Treatment Form) <b>(T2)</b>  |  |
| Films/DRRs (simulation and portal) <b>(T3)</b>         |  |
| Calculations <b>(T4)</b>                               |  |
| Planning CT (MRI, PET) scan <b>(C1)</b>                |  |
| <b><u>Final Dosimetry Information:</u></b>             | Within 1 week of RT end  |
| Daily Treatment Record <b>(T5)</b>                     |  |
| Isodose Distribution (including color DVH) <b>(T6)</b> |  |
| Boost Films (simulation and portal) <b>(T8)</b>        |  |
| Radiotherapy Form <b>(T1)</b>                          | Week 13 (Day 90 from the start of radiation therapy)   |
| Treatment Form <b>(TF)</b>                             |  |
| Post-Treatment Evaluation Form <b>(F0)</b>             |  |
| Follow-Up Form <b>(F1)</b>                             | Begin at 6 months from start of treatment, then q 3 months x 2 years, q 6 months x 3 years, then annually. Also at progression/relapse and at death. |
| Adverse Event Form <b>(AE)</b>                         | As applicable for toxicity assessment reporting.   |

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints**

#### **13.1.1 Primary Endpoint (9/7/05)**

- Acute treatment-related toxicity in patients with her2/neu overexpression or not treated with paclitaxel ± trastuzumab and concurrent radiation therapy as defined by one of the following:
  - Grade 4 neutropenia or grade 4 febrile neutropenia
  - Grade 3 diarrhea, grade 3 nausea, or grade 3 vomiting
  - Grade 3 thrombocytopenia or grade 3 for all of the following non-hematologic toxicities: renal, pulmonary, hepatic, or neurologic toxicity
  - Grade 3 rectal or genitourinary bleeding
  - Grade 3 left ventricular failure or grade 2 for all other cardiac toxicity
  - Inability to complete the chemoradiation due to treatment-related toxicity

#### **13.1.2 Secondary Endpoints**

- Treatment completion
- Complete response to treatment at 12 weeks
- Disease-free and overall survival
- Collection of pretreatment and post-treatment tissue specimens for translational studies and correlation with response and clinical outcome

### **13.2 Sample Size**

**13.2.1 Patient Groups:** There are two separate and independent patient groups as defined by the her2/neu analysis: those patients who have her2/neu overexpression (Group 1), and those who do not (Group 2). The two groups will receive different therapy per protocol (paclitaxel ± trastuzumab and concurrent radiation therapy). Patients with her2/neu overexpression will receive paclitaxel and trastuzumab along with daily irradiation, and those without her2/neu overexpression will receive paclitaxel along with daily irradiation in an identical fashion but will have trastuzumab omitted from their therapy.

**13.2.2 Sample Size Derivation (9/7/05):** The primary goal of this phase I/II bladder study is to estimate the acute treatment-related toxicity (defined in 13.1.1) in each group of patients as described in 13.2.1. To calculate sample size, we estimate that 10% of patients in each group will experience an acute treatment-related toxicity as defined in 13.1.1. Using Fleming's one-sample multiple test procedure<sup>42</sup> with Type I and II errors each set at 10%, we would require 40 analyzable cases for each group to reject a null hypothesis that the true toxicity rate to this therapy is greater than 25% in favor of the alternative hypothesis that the true rate is no more than 10%. Adjusting that number of cases by 10% for ineligible or inevaluable (no data) cases, the primary endpoint requires at least 44 cases for each patient group. **The total sample size for the study will be 88.**

### **13.3 Patient Accrual**

Based upon patient accrual in previous RTOG bladder studies (RTOG 97-06 and 99-06), there will be relatively few entries during the initial 6 months while institutions are obtaining IRB approval. The patient accrual is projected to be about 3 patients per month. We expect to complete the accrual in 3 years. However, we also expect that accrual might be better and thus would result in completing the study earlier. Accrual rates may differ between the two patient groups. If both groups achieve the proposed sample size (44 each) at the same time, patient accrual to both groups will be closed. If one group has reached the targeted sample size (n = 44), patient accrual for that group will be closed while accrual to the other group will continue until it also achieves its proposed 44 patients. If at 24 months after study activation the average monthly accrual between months 18 and 24 is less than 1 patient in either group, the feasibility of completing the study will be discussed with the study chairs, disease site chair, and RTOG Research Strategy Committee.

### **13.4 Analysis Plan**

This is a non-randomized phase I/II trial with two patient groups (Group 1 and Group 2) based on her2/neu overexpression. Analysis on comparisons between the two groups will not be performed. All analyses will be carried out for each patient group separately.

#### **13.4.1 Interim Reports:**

Interim reports will be prepared every 6 months until the final analysis. In general, the interim reports will 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 protocol treatment (paclitaxel ± trastuzumab and concurrent radiation therapy).

**13.4.2** CDUS Reporting:

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

**13.4.3** Significance Testing for Early Termination and Reporting (9/7/05):

Severe toxicity is defined as grade 2 or higher in cardiac toxicity (grade 3 or higher in left ventricular failure), or grade 3 or higher in other toxicities as defined in Section 13.1.1 due to protocol treatment. The following early stopping rules are proposed to test the null hypothesis that the proportion of severe toxicity is greater than or equal to 25% with significance level 0.10, within each patient group.

In the first 6 eligible and evaluable patients of group 1 (those treated with paclitaxel, trastuzumab and concurrent radiation therapy), if we observe 3 or more severe toxicities, we will conclude that the proportion of severe toxicity is greater than 10%. Regardless of the severe toxicity information reported in group 2 patients, the study statistician will then recommend to the study chairs, disease site chair, and RTOG Research Strategy committee that accrual be temporarily suspended. After the data has been reviewed by the study chairs and disease site chair, the appropriate further action will be taken. If we observe less than 3 toxicities, then the trial will continue as planned, and the following 2 additional analyses in these patients will be done:

- 5 or more severe toxicities out of the first 23 eligible and evaluable patients, or
- 6 or more severe toxicities out of the first 40 eligible and evaluable patients.

A similar analytic plan of toxicity will be applied to group 2 patients (those without her2/neu overexpression). Since toxicity in group 1 patients would be expected to be as much as toxicity in group 2 patients after the addition of trastuzumab in that group: In the event that there are 3 or more severe toxicities in group 2 without the first 6 eligible and evaluable patients in group 1, the study statistician will still recommend to the study chairs, disease site chair, and RTOG Research Strategy Committee that the accrual be temporarily suspended for data review. Further appropriate action will then be taken accordingly.

If 3 or more patients experience cardiac SAEs at any point during the trial, accrual will be temporarily suspended. Data will then be reviewed with the study chairs, disease site chair, RTOG Research Strategy Committee, FDA, and CTEP to determine whether inclusion/exclusion criteria require modification. Further appropriate action will then be taken accordingly.

**13.4.4** Analysis for Reporting Initial Treatment Results (9/7/05):

The primary endpoint of this study is the acute treatment-related toxicity as defined in Section 13.1.1: (1) in patients who have her2/neu overexpression and are treated with paclitaxel, trastuzumab, and concurrent radiation therapy and (2) in patients who do not have her2/neu overexpression and are treated with paclitaxel and concurrent radiation therapy alone. To examine this, the analysis will be carried out when each eligible and evaluable patient has had at least 90 days of follow-up from the start of protocol treatment. For each patient group, the number of patients will be tabulated by the type and grade of toxicity. If we observe the number of cases with the treatment-related toxicities defined in 13.4.3, toxicity data will be reviewed and appropriate actions will be recommended by the study chair, disease chair, and statisticians to RTOG Research Strategy Committee.

Grade 2+ toxicity rate will be computed as the number of cases with grade 2+ maximum toxicity divided by the total number of patients who have completed chemotherapy and radiation therapy. One-sided Z-test based on normal approximation will be used to test the toxicity hypothesis.

Study secondary outcomes, disease-free and overall survival, will be calculated using the Kaplan-Meier method.<sup>43</sup> All eligible and evaluable patients will be included in a secondary outcome analyses. All failure time variables will be measured by the time interval from the date of treatment started to the date of the failure event. For disease-free survival, the progression-

free survival will be measured from the date of treatment started to the date of documentation of progression or until the date of death. This endpoint includes all measures of disease including physical exam, CT scans, and biopsies. For all secondary endpoints, all patients will be followed for a minimum of 5 years.

The number of patients within each group who completed treatment will be reported. The complete response rate at 12 weeks will also be reported.

**13.5 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 between men and women, or whites and non-whites, will be investigated. Prior RTOG bladder cancer trials, 89-03, 95-06 and 97-06 accrued about 6% non-whites and 21% women. With the proposed 44 evaluable patients per group, there will not be enough statistical power to detect the difference in the primary endpoint between race groups and/or gender groups. Nonetheless, the descriptive statistics for each of these groups will be reported.

**GENDER AND MINORITY ACCRUAL ESTIMATES FOR EACH PATIENT GROUP**

**Patients With Her2/Neu Overexpression**

| Ethnic Category                                | Sex/Gender |       |         |            |
|--|------------|-------|---------|------------|
|  | Females    | Males | Unknown | Total      |
| Hispanic or Latino                             | 0          | 1     | 0       | 1          |
| Not Hispanic or Latino                         | 9          | 34    | 0       | 43         |
| Unknown  | 0          | 0     | 0       | 0          |
| <b>Ethnic Category: Total of all subjects*</b> | 9          | 35    | 0       | <b>*44</b> |
| Racial Category                                |            |       |         |            |
| American Indian or Alaskan Native              | 0          | 0     | 0       | 0          |
| Asian  | 0          | 0     | 0       | 0          |
| Black or African American                      | 0          | 1     | 0       | 1          |
| Native Hawaiian or other Pacific Islander      | 0          | 0     | 0       | 0          |
| White  | 9          | 34    | 0       | 43         |
| More than one race                             | 0          | 0     | 0       | 0          |
| Unknown  | 0          | 0     | 0       | 0          |
| <b>Racial Category: Total of all subjects*</b> | 9          | 35    | 0       | <b>*44</b> |

**Patients Without Her2/Neu Overexpression**

| Ethnic Category                                | Sex/Gender |       |         |            |
|--|------------|-------|---------|------------|
|  | Females    | Males | Unknown | Total      |
| Hispanic or Latino                             | 0          | 1     | 0       | 1          |
| Not Hispanic or Latino                         | 9          | 34    | 0       | 43         |
| Unknown  | 0          | 0     | 0       | 0          |
| <b>Ethnic Category: Total of all subjects*</b> | 9          | 35    | 0       | <b>*44</b> |
| Racial Category                                |            |       |         |            |
| American Indian or Alaskan Native              | 0          | 0     | 0       | 0          |
| Asian  | 0          | 0     | 0       | 0          |
| Black or African American                      | 0          | 1     | 0       | 1          |
| Native Hawaiian or other Pacific Islander      | 0          | 0     | 0       | 0          |
| White  | 9          | 34    | 0       | 43         |
| More than one race                             | 0          | 0     | 0       | 0          |
| Unknown  | 0          | 0     | 0       | 0          |
| <b>Racial Category: Total of all subjects*</b> | 9          | 35    | 0       | <b>*44</b> |

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## **APPENDIX I (9/7/05)**

**RTOG 0524**

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

**A PHASE I/II TRIAL OF A COMBINATION OF PACLITAXEL AND TRASTUZUMAB WITH DAILY IRRADIATION OR PACLITAXEL ALONE WITH DAILY IRRADIATION FOLLOWING TRANSURETHRAL SURGERY FOR NON-CYSTECTOMY CANDIDATES WITH MUSCLE-INVASIVE BLADDER CANCER**

**This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.**

**You are being asked to take part in this study because you have bladder cancer and are not able to have surgery to remove your bladder.**

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

The purpose of this study is to find out what effects (good and bad) chemotherapy combined with external radiation therapy has on you and your cancer. The chemotherapy drugs (paclitaxel and trastuzumab) used in this study are not experimental drugs. However, the use of trastuzumab in bladder cancer is experimental, as is the combination of trastuzumab plus chemotherapy and radiation (chemoradiation). These drugs have been used separately in the treatment of many patients with tumors such as yours, but this is the first study in humans that is using the combination of trastuzumab plus chemoradiation. This research study is being done because we do not know whether this combination of drugs with radiation is a safe and effective therapy for your type of cancer.

The usual treatment for your type of bladder cancer is surgical removal of the bladder and the surgical construction of an alternative bladder that usually requires a permanent opening (stoma) in your abdomen for urine drainage. Many patients like you may have difficulty undergoing this major surgical procedure. The combination of chemotherapy and radiation may be an effective alternative treatment in patients unable to undergo surgery.

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

About 88 people will take part in this study.

## **WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY? (9/7/05)**

### **Pre-Study (11/7/06) (8/12/09)**

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

- Your doctor will obtain your complete medical history, perform a complete physical examination, evaluate your ability to carry out daily activities, and record your weight, vital signs (body temperature, heart rate, breathing rate, and blood pressure) and your body surface area.
- Blood samples (approximately 3 teaspoons of blood) will be drawn for hematology, serum chemistry, and coagulation in order to check for blood cell counts and organ function.
- Urine will be collected for routine urinalysis.
- An x-ray or CT scan of the chest will be done.
- A CT scan of the abdomen, and pelvis will be done.
- A bone scan will be done, if recommended by your study doctor.
- A pregnancy test, if you are able to become pregnant, will be done.
- An examination and minor surgical procedure called a transurethral bladder resection (TURB) will be performed. Under sedation (anesthesia), the doctor feels your bladder and then a lighted tube is inserted through the urethra (the small tube-like structure that allows urine to empty from the bladder) into the bladder. The surgeon examines your bladder tumor through this fiberoptic scope. The surgeon then will remove your tumor as thoroughly as is safely possible using an electric current. Some of your tissue around the tumor also will be removed for biopsy.

The following tests are study specific and are being done only because you have consented to being in this study.

- A test that evaluates how well your heart chambers fill with blood and pump it to the rest of the body (A MUGA scan or echocardiogram).
- A 12-lead electrocardiogram (ECG), which tests the electrical activity of the heart.
- Laboratory analysis of a sample of your tumor to determine certain characteristics of your cancer (her2/neu analysis); the outcome of this analysis will determine whether you receive paclitaxel alone or paclitaxel plus trastuzumab.

### **During the Study**

If these tests and evaluations indicate that you are eligible for this study and you agree to participate, you will receive daily radiation treatments to the bladder for 7 weeks for 5 days a week. In addition, you will receive weekly chemotherapy either with paclitaxel alone or with paclitaxel with trastuzumab. This will depend on certain characteristics of your cancer that are examined in the laboratory. Chemotherapy will be given intravenously once a week, and this will take between 1 and 4 hours each week. Regardless of which treatments you receive, you will need the tests and procedures listed below. They are part of regular cancer care.

During the course of your radiation and chemotherapy treatments, you will receive radiation treatments daily as an outpatient, for 5 days a week, except hospital holidays. In addition, you will need to visit the outpatient oncology clinic once a week for study procedures and chemotherapy. The chemotherapy and radiation treatments will take about 7 weeks to complete. Your doctor will inform you of any additional visits you will need to make. During your weekly visits, the following tests will be performed:

- Physical examination of the major body systems and recording of your weight.
- Recording of vital signs (body temperature, heart rate, breathing rate, and blood pressure) and assessment of performance status (your ability to perform daily activities of living).
- Blood will be drawn for testing of blood counts and organ function.

The total volume of blood drawn will be between 16.5 mL and 41 mL (1 to 3 tablespoons) per week.

During the study, you will be followed for any potential side effects of the study treatments. Your dose of chemotherapy may be reduced if side effects occur. If the side effects are severe enough, the doctor may temporarily stop chemotherapy and/or radiation, reduce the dose again, or stop the treatments completely.

The study doctor may require that you have additional tests if medically indicated.

### **End of Study Treatment (8/12/09)**

When you stop or complete the study treatment, you will be asked to return to the clinic for an end of treatment visit.

- At this visit a series of tests will be performed that are similar to the initial (pre-study) tests.
- A few weeks after the completion of the chemotherapy and radiation, the surgeon will re-examine your bladder through the fiberoptic scope and perform a biopsy to make sure the tumor has been fully treated.
- Additionally, a few weeks after completion of treatment, and if recommended by your study doctor, you will undergo a bone scan, a CT scan of the abdomen and pelvis, and an x-ray or CT scan of the chest.

Thereafter, you should undergo careful and frequent evaluations of the bladder through a fiberoptic scope, as well as occasional CT scans. These tests are part of regular cancer care, and not specific to this study. Should the bladder tumor come back or get bigger, surgical removal of your bladder may be recommended.

### **HOW LONG WILL I BE IN THE STUDY? (8/12/09)**

You will be in the study for about 2 months of treatment. Treatment will begin 3 to 8 weeks after the minor bladder surgery and will take about 7 weeks to complete. A few weeks after the completion of the chemotherapy and radiation, the surgeon will re-examine your bladder. Follow-up visits will take place at 6 months from the start of treatment, every 3 months for 2 years, every 6 months for 3 years, and once a year for your lifetime.

Your doctor may decide to take you off this study if your doctor believes it is in your medical best interest, if funding for this study is stopped, or if your condition worsens. You may also be taken off this study if new information becomes available about how to better prevent growth of bladder cancer.

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.

### **CAN I STOP BEING IN THE STUDY?**

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will discuss with you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the drugs or radiation can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

### **WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY? (9/7/05)**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs or intervention. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

### **Risks and side effects associated with radiation therapy to the pelvis include those that are: (8/12/09)**

#### Likely

- Loss of pubic hair
- Reddening and irritation of the skin in the treatment area
- Diarrhea
- Urinary frequency, possibly with pain and/or blood
- Tiredness near the end of treatment
- Nausea and/or vomiting
- Poor digestion of food
- Rectal irritation
- Pain with sexual intercourse
- Shortening and narrowing of the vagina

- Low blood counts causing easy bruising
- Radiation to the pelvis will cause sterility. Women of childbearing potential will go through menopause and may require the use of hormones given orally to replace the hormones normally produced by the ovaries.

#### Less Likely

- Weight loss; if this is severe, you may need a tube placed into your stomach to provide nutrition
- Rectal ulcer
- Bleeding or narrowing of the rectum

#### Rare But Serious

- Bleeding and/or blockage of the bowel, which may require surgery
- Bowel perforation (hole in small or large intestine), which may require emergency surgery and which can result in death
- Ureteral (tube connecting kidneys to the bladder) obstruction
- Fistula (opening) forming between pelvic tissues

### **Risks and side effects associated with paclitaxel include those that are:**

#### Likely

- Decrease in blood counts, which can lead to a risk of infection and bleeding
- Hair loss
- Fatigue
- Mouth sores
- Numbness, tingling, or burning in the hands or feet
- Skin redness or rash

#### Less Likely

- Muscle aches and/or joint pains
- Nausea and/or vomiting
- Headaches
- Skin or nail darkening
- Skin ulcers

#### Rare But Serious

- Changes in vision
- Decrease in blood pressure
- Allergic reaction, which can cause difficulty breathing, irregular heartbeat, low blood pressure, and even be life threatening
- Continuing, long-lasting numbness, tingling, or burning in the hands or feet
- Severe rash called Stevens-Johnson syndrome, which can cause fever and red sores in your mouth and eyes
- Bradycardia (slow heart rate)

## **Risks and side effects associated with trastuzumab include those that are:**

### **Likely**

- Fatigue
- Diarrhea
- Dizziness
- Pain in your back, abdomen, at the site of your tumor, and/or at the site of the trastuzumab injection
- Flu-like symptoms
- Abnormalities in liver function tests
- Leukopenia (decrease in white blood cell counts, which can lead to a risk of infection)  
NOTE: This side effect is likely when trastuzumab is used in combination with paclitaxel, as it is in this study. When trastuzumab is given alone, the risk of leukopenia is less likely.

### **Less Likely**

- Muscle aches and/or joint pains
- Nausea and/or vomiting
- Loss of appetite
- Sores in your mouth
- Headaches
- Allergic reaction, which can cause difficulty breathing, hives, or rashes
- Abnormality in red blood cell counts
- Heart damage causing heart failure or irregular heartbeat. The risk of heart damage may be greater in patients who have lower than normal readings on the pre-study test of heart function.

### **Rare But Serious**

- 
- Life threatening allergic reaction with difficulty breathing, irregular heartbeat or low blood pressure
- Severe lung problems: There have been rare cases of severe lung problems in patients who received trastuzumab. Some of these patients died. Most of the cases occurred in patients who had other lung problems such as spread of their cancer to the lungs, although some occurred in patients without previous disease the lungs.

### **Overall Risks**

Trastuzumab with chemoradiation has not been previously tested. There is potential risk of unknown side effects or enhancement of known side effects associated with radiation and with any of the drugs used in this study.

### **Reproductive Risks**

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Patients receiving trastuzumab should also not become pregnant or father a baby for 6 months after the last trastuzumab dose. Women should not breastfeed a baby while on this study,

and women receiving trastuzumab should continue without breastfeeding for 6 months after the last trastuzumab dose. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Radiation therapy to the pelvis will result in sterility in women. In men, the testes can be protected during radiation treatments.

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

Taking part in this study may or may not make your health better. While doctors hope the study treatment will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the study treatment as a treatment for cancer. This information could help future cancer patients.

### **WHAT OTHER CHOICES TO I HAVE IF I DO NOT PARTICIPATE IN THIS STUDY?**

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting radiation therapy, chemotherapy with standard drugs such as cisplatin, or surgery; these options may be given either alone or in combination with each other
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

### **WILL MY MEDICAL RECORDS BE KEPT PRIVATE? (11/7/06)**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- Qualified representatives of Genentech, Inc., the company that makes trastuzumab
- Local institutional research boards
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials

### **WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?**

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

Paclitaxel is commercially available.

The Division of Cancer Treatment and Diagnosis at NCI will provide you with the NCI-sponsored/supplied agent (trastuzumab) free of charge for this study. Every effort will be made to ensure adequate supplies of the sponsored/supplied agent, free of charge, for all participants. If the drug becomes commercially available for this indication there is a remote possibility that you may be asked to purchase subsequent supplies. Your physician will discuss this with you should this situation arise.

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

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

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

### **WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?**

It is important that you tell your study doctor, \_\_\_\_\_ [*investigator's name(s)*], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at \_\_\_\_\_ [*telephone number*].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

### **WHAT ARE MY RIGHTS IF I PARTICIPATE IN THIS STUDY?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

### **WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY ?**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_ [name(s)] at \_\_\_\_\_ [telephone number].

For questions about your rights while taking part in this study, call the \_\_\_\_\_ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

\*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [\*Only applies to sites using the CIRB.]

**Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.**

Consent Form for Use of Tissue for Research

### **About Using Tissue for Research**

You have had a biopsy (or surgery) to see if you have cancer. Your doctor has removed some tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer. Please read the information sheet called “How is Tissue Used for Research” to learn more about tissue research. This information sheet is available to all at the following web site:  
<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>

The research that may be done with your tissue is not designed specifically to help you. It might help people who have bladder tumors and other diseases in the future. Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. This research will not have an effect on your care.

## **Things to Think About**

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.

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

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

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

## **Benefits**

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

## **Risks**

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

## **Making Your Choice**

Please read the sentence below and think about your choice. After reading the sentence circle “Yes” or “No”. If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB’s phone number.

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

1. My tissue/blood may be used for research about cancer.

Yes

No

## **Where Can I Get More Information?**

**You may call the National Cancer Institute’s Cancer Information Service at**

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

You may also visit the NCI web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

### Signature

I have been given a copy of all\_\_*[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

\_\_\_\_\_

Participant (or Legal Representative)

\_\_\_\_\_

Date

\_\_\_\_\_

Investigator's Signature

\_\_\_\_\_

Date

**APPENDIX II (8/12/09)**

**ZUBROD PERFORMANCE SCALE**

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

### APPENDIX III

## AJCC Staging System, 6<sup>th</sup> Edition Bladder

### DEFINITION OF TNM

#### Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Ta Noninvasive papillary carcinoma
- Tis Carcinoma *in situ*: "flat tumor"
- T1 Tumor invades subepithelial connective tissue
- T2 Tumor invades muscle
  - T2a Tumor invades superficial muscle (*inner half*)
  - T2b Tumor invades deep muscle (*outer half*)
- T3 Tumor invades perivesical tissue
  - T3a microscopically
  - T3b macroscopically (*extravesical mass*)
- T4 Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
  - T4a Tumor invades the prostate, uterus, vagina
  - T4b Tumor invades the pelvic wall, abdominal wall

#### Regional Lymph Nodes (N)

Regional lymph nodes are those within the true pelvis; all others are distant nodes.

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single lymph node, 2 cm or less in greatest dimension
- N2 Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3 Metastasis in a lymph node more than 5 cm in greatest dimension

#### Distant Metastasis (M)

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

### STAGE GROUPING

|           |     |    |    |
|-----------|-----|----|----|
| Stage 0a  | Ta  | N0 | M0 |
| Stage 0is | Tis | N0 | M0 |
| Stage I   | T1  | N0 | M0 |
| Stage II  | T2a | N0 | M0 |
|           | T2b | N0 | M0 |
| Stage III | T3a | N0 | M0 |
|           | T3b | N0 | M0 |
|           | T4a | N0 | M0 |

**APPENDIX III (continued)**  
**AJCC Staging System, 6<sup>th</sup> Edition**  
**Bladder**

|          |       |       |    |
|----------|-------|-------|----|
| Stage IV | T4b   | N0    | M0 |
|          | Any T | N1    | M0 |
|          | Any T | N2    | M0 |
|          | Any T | N3    | M0 |
|          | Any T | Any N | M1 |

**HISTOPATHOLOGIC TYPE**

The histologic types are:

Transitional cell carcinoma (*urothelial*)

*In situ*

Papillary

Flat

With squamous metaplasia

With glandular metaplasia

With squamous and glandular metaplasia

Squamous cell carcinoma

Adenocarcinoma

Undifferentiated carcinoma

**HISTOPATHOLOGIC GRADE (G)**

GX Grade cannot be assessed

G1 Well differentiated

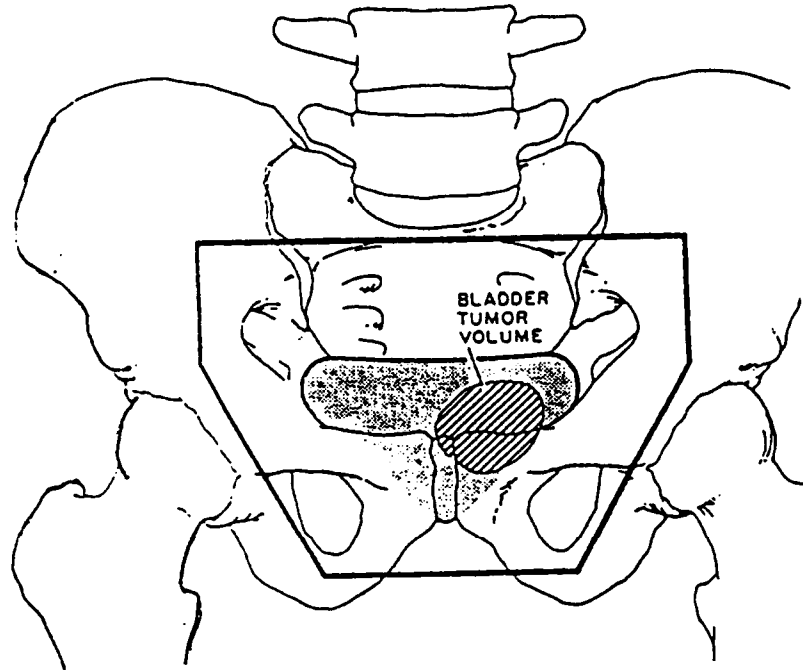
G2 Moderately differentiated

G3-4 Poorly differentiated or undifferentiated

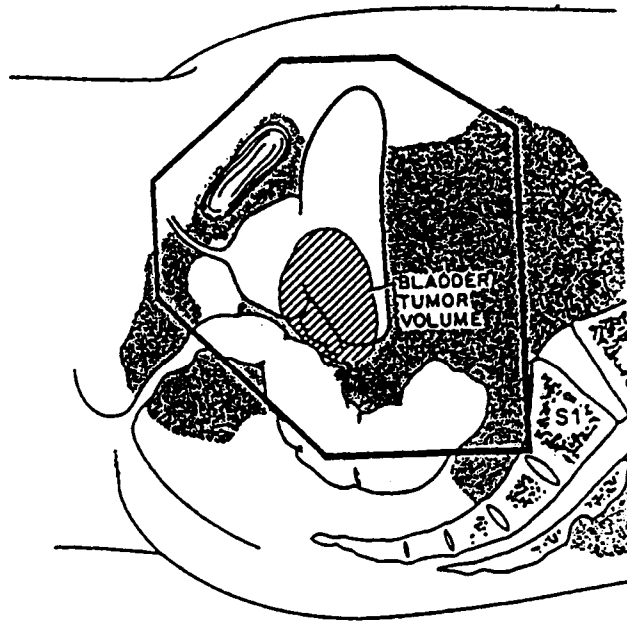
APPENDIX IV

SMALL PELVIC FIELDS

Anterior View



Lateral View



**APPENDIX V**

**SAMPLE CYTOSCOPY REPORT FORM**

**See Section 3.1.2.**

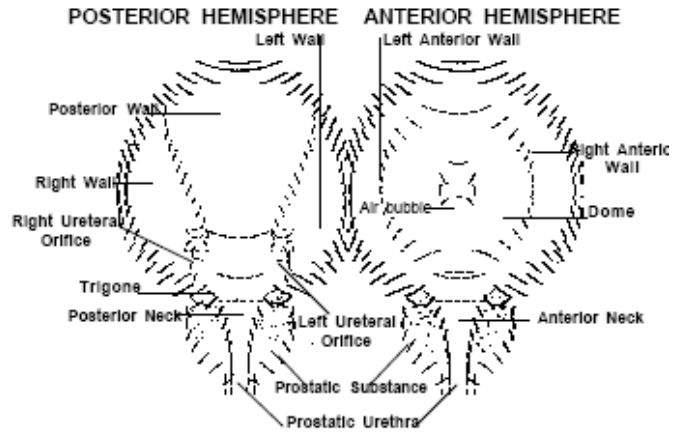
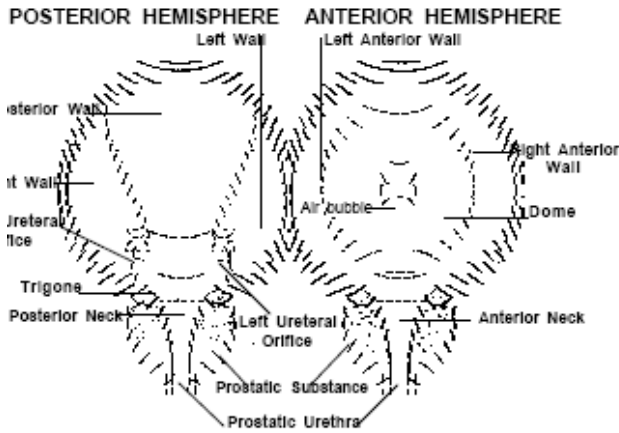
**This is an example of information that will be collected on the Initial Evaluation (I1) Form.**

Cytoscopy Date: \_\_\_\_\_ Surgeon: \_\_\_\_\_  
 Specify location/origin of primary (at cysto or TURB): \_\_\_\_\_  
 Visibly complete TURB? Yes No  
 Palpable mass or induration persists after TURB? Yes No  
 Initial largest tumor (diameter): ≤1 cm 1.1-2.9 cm 3-4.9 cm ≥5 cm  
 Dose tumor invade prostate or vagina? Yes No  
 Is tumor fixed to pelvic/abdominal wall? Yes No

Please complete the following two diagrams:

**A. TUMOR LOCATION BEFORE TURB.**

**B. POST-TURB: IF MACROSCOPIC TUMOR REMAINS AT END OF PROCEDURE, INDICATE ITS LOCATION. IF NOT, CHECK "NONE."**



NONE

## APPENDIX VI (1/9/07)

### CTSU LOGISTICS

#### ADDRESS AND CONTACT INFORMATION FOR RTOG-0524

| <b>To submit site registration documents:</b>   | <b>For patient enrollments:</b>   | <b>Submit study data directly to the RTOG unless otherwise specified in the protocol:</b>  |
|---|---|--|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone - 1-888-823-5923<br>Fax – 215-569-0206  | CTSU Patient Registration<br>Voice Mail – 1-888-462-3009<br>Fax – 1-888-691-8039<br>Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays)<br><br>[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.] | RTOG Headquarters<br>1818 Market Street, Suite 1600<br>Philadelphia, PA 19103<br><br>Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. |
| <b>For patient eligibility questions:</b><br>Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214.   |   |  |
| <b>For treatment-related questions:</b><br>Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page.   |   |  |
| <b>For questions unrelated to patient eligibility, treatment, or data submission</b> contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a> . All calls and correspondence will be triaged to the appropriate CTSU representative. |   |  |
| <b>The CTSU Public Web site</b> is located at: <a href="http://www.ctsu.org">www.ctsu.org</a>   |   |  |
| <b>The CTSU Registered Member Web site</b> is located at: <a href="http://members.ctsu.org">http://members.ctsu.org</a>   |   |  |

## CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

### REGISTRATION/RANDOMIZATION

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

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

All forms and documents associated with this study can be downloaded from the RTOG-0524 Web page on the CTSU registered member Web site (<http://members.ctsu.org>). Patients can be registered only after pre-treatment

## APPENDIX VI (Continued)

evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

### Requirements for RTOG-0524 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

Note: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

### Pre-study requirements for patient enrollment on RTOG-0524

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.
- This protocol requires a 2-Step registration process. Pathology materials for her2/neu analysis and tissue banking must be submitted within three weeks of initial registration per section 10.2 of the protocol. Once the results of the her2/neu analysis is obtained, registration must be completed by entering the results into the second step eligibility checklist.

### CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

Step 1:

- CTSU Patient Enrollment Transmittal Form
- RTOG-0524 Step 1 Eligibility Checklist

Step 2:

- CTSU Patient Enrollment Transmittal Form
- RTOG 0524 Step 2 Eligibility Checklist

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that RTOG registration hours end at 4:30 pm Eastern Time. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG (**within the confines of RTOG's registration hours**) to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax. Treatment arms will be assigned only after the results of the her2/neu analysis have been entered and submitted with eligibility checklist #2. The CTSU registrar will confirm registration by fax or e-mail.

Protocol treatment should begin within 3 to 8 weeks following transurethral bladder tumor resection (TURB).

## APPENDIX VI (Continued)

### DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0524 web page located on the CTSU registered member Web site (<http://members.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU.
3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the RTOG.

### SPECIAL MATERIALS OR SUBSTUDIES

#### Specimen Collection for correlatives or banking (Protocol Section 10.0)

- Collect, prepare, and submit specimens as outlined in the protocol
- Do not send specimens, supporting clinical reports, or transmittals to the CTSU
- CTSU Institutions qualify for specimen reimbursement as described in Section 10.3 of the protocol. Payments will be made in accordance with RTOG's pathology payment cycle and forwarded to the enrolling sites by the Cooperative Group credited with the accrual.

#### Specimen Banking:

- Provided patient consent is obtained sent to the investigator, specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it. See Section 10.4.2

#### Radiation Therapy (Protocol Section 6.0):

- Please consult section 6.0 of the protocol for specific information regarding radiation therapy.

**NOTE:** Radiation Therapy quality assurance is required for this protocol. A planning CT scan of the pelvis and initial small pelvis port films must be submitted to RTOG headquarters within 7 working days of initiation of treatment. Weekly ports are also required for all fields but may be substituted with other forms of target localization. Please follow the instructions provided in section 6.6 of the protocol. See protocol section 12.1 for a complete inventory of dosimetry items to be submitted.

#### Radiation Therapy Quality Assurance Reviews (Protocol Section 6.9):

- The Radiation Oncology Co-Chair will perform an RT Quality Assurance Review. See section 6.9 for full details.

### SERIOUS ADVERSE EVENT (SAE) REPORTING

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (<http://members.ctsu.org>) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG-0524 web page.
3. Do not send adverse event reports to the CTSU.

## APPENDIX VI (Continued)

### DRUG PROCUREMENT

Investigational Agents: Trastuzumab (Herceptin®)

Commercial Agents: Paclitaxel (Taxol®)

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in sections 7.2 and 7.3 of the protocol.

2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the RTOG 0524 Web page.

### REGULATORY AND MONITORING

#### Study Audit

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

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

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

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

#### Health Insurance Portability and Accountability Act of 1996 (HIPAA)

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

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

#### Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.