RADIATION THERAPY ONCOLOGY GROUP
RTOG 1010

A PHASE III TRIAL EVALUATING THE ADDITION OF TRASTUZUMAB TO TRIMODALITY TREATMENT OF HER2-OVEREXPRESSING ESOPHAGEAL ADENOCARCINOMA

NCI-Supplied Agent: Trastuzumab (NSC 688097; IND 6667)

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Document History

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1-800-227-5463, ext. 4189

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Institutions not aligned with 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 Members’ side of the website located at https://www.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 unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.

- Data query and delinquency reports will be sent directly to the enrolling site by RTOG by mail as directed in the Study Contacts table. Please send query responses and delinquent data to 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 IAM account contact information current. This will ensure timely communication between the clinical site and the RTOG data center.
<table>
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<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
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<td>CTSU Regulatory Office</td>
<td>CTSU Patient Registration</td>
<td>RTOG Headquarters \ 1818 Market St., Suite 1600 \ Philadelphia, PA 19103 \ Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
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<tr>
<td>1818 Market Street, Suite 1100</td>
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<td>Philadelphia, PA 19103</td>
<td>Fax – 1-888-691-8039</td>
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<tr>
<td>Phone – 1-866-651-CTSU</td>
<td>Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays)</td>
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<td>Fax – 215-569-0206</td>
<td>[Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]</td>
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**For patient eligibility or treatment-related questions** Contact the Study PI of the Coordinating Group.

**For questions unrelated to patient eligibility, treatment, or data submission** contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

**For detailed information on the regulatory and monitoring procedures for CTSU sites** please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website [https://www.ctsu.org](https://www.ctsu.org)

**The CTSU Web site is located at:** [https://www.ctsu.org](https://www.ctsu.org)

CTSU logistical information is located in Appendix VIII.
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RADIATION THERAPY ONCOLOGY GROUP

RTOG 1010

A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma

SCHEMA

STEP 1 REGISTRATION

HER2 Testing
Mandatory submission of tissue for HER2 testing

NOTE: Tumor tissue must be received and patients must have confirmed HER2 positivity before randomization can occur. Patients with confirmed HER2 negativity will not be randomized.

STEP 2 REGISTRATION

STRATIFY
Presence of adenopathy: No vs Yes—celiac absent vs. Yes—celiac present ≤ 2 cm

RANDOMIZE

Arm 1
Radiation (50.4 Gy), paclitaxel, carboplatin, and trastuzumab
Followed by surgery 5-8 weeks after completion of radiation
Then maintenance trastuzumab, every 3 weeks for 13 treatments

Arm 2
Radiation (50.4 Gy), paclitaxel, and carboplatin
Followed by surgery 5-8 weeks after completion of radiation

Patient Population: (See Section 3.0 for Eligibility)
Pathologically confirmed HER2 expressing adenocarcinoma of the esophagus centrally assessed within 56 days prior to Step 2 registration; primary adenocarcinoma of the esophagus involving the mid (up to 25 cm), distal and/or esophagogastric junction.

Required Sample Size: 160
______ (Y) 1. Does the patient have a histologically confirmed primary adenocarcinoma of the esophagus that involves the mid (up to 25 cm), distal, or esophagogastric junction? (Extension into the stomach, up to 5 cm, is allowed.)

______ (Y) 2. Did the patient have an endoscopy with biopsy?

______ (Y) 3. Will the patient’s tissue be submitted for HER2 testing?

______ (Y/N) 4. Based on the CT scan of the chest/abdomen/pelvis or whole-body PET/CT does the patient have regional adenopathy that includes para-esophageal, gastric, gastrohepatic, and celiac nodes?
   __________(Y/NA) If celiac nodes are involved are they ≤ 2 cm?

______ (Y) 5. Based on the CT scan of the chest/abdomen/pelvis or whole-body PET/CT and endoscopy is the patient’s preliminary cancer stage, according to the AJCC 7th edition staging, either T1N1-2, T2-3N0-N2?

______ (N) 6. Based on the CT scan of the chest/abdomen/pelvis or whole-body PET/CT and endoscopy does the patient have distant metastases?

______ (Y) 7. Is the patient’s Zubrod performance status 0-2?

______ (Y) 8. Is the patient at least 18 years of age?

______ (Y) 9. Does the patient have adequate bone marrow function as specified in Section 3.1?

______ (Y) 10. Do the patient’s other laboratory values meet the criteria in Section 3.1?

______ (Y/NA) 11. For women of childbearing potential, was a serum or urine pregnancy test completed within 14 days of registration?
   __________(Y) If yes, was the pregnancy test negative?

______ (Y/NA) 12. If a women of childbearing potential or a sexually active male, is the patient willing to practice adequate contraception while on study and for at least 60 days after the last dose of chemotherapy or trastuzumab?

______ (Y) 13. Did the patient provide study specific informed consent prior to study entry?

______ (N) 14. Does the patient have cervical esophageal carcinoma?

______ (N) 15. Has the patient had prior chemotherapy for esophageal cancer?

______ (N) 16. Has the patient had prior radiation for esophageal cancer or prior chest radiotherapy?

______ (N) 17. Has the patient had prior anthracycline or taxane?

______ (N) 18. Is there evidence of tracheoesophageal fistula or invasion into the trachea or major bronchi?

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ELIGIBILITY CHECKLIST—STEP 1 (12/30/10)

Case # ________ (page 2 of 3)

_______(N/Y) 19. Has the patient had prior invasive malignancies, except for non-melanomatous skin cancers?

_______(Y) If yes, has the patient been disease free for $\geq 2$ years?

_______(N) 20. Has the patient had prior therapy that directly targets the HER1 (EGFR) and/or the HER2 pathway?

_______(N) 21. Has the patient had prior trastuzumab?

_______(N) 22. Has the patient had allergic reactions to the study drugs involved in this protocol or to a monoclonal antibody?

_______(N) 23. Does the patient have a history of congestive heart failure?

_______(N) 24. Does the patient have severe, active co-morbidity, as defined in Section 3.2?

_______(N) 25. Is the patient pregnant or lactating?

The following questions will be asked at Study Registration for STEP 1:

3DCRT credentialing is required for this protocol

__________ 1. Institutional person randomizing case

__________ (Y) 2. Has the STEP 1 Eligibility Checklist been completed?

__________ (Y) 3. In the opinion of the investigator, is the patient eligible?

__________ 4. Date informed consent signed

__________ 5. Participant Initials (First Middle Last)

__________ 6. Verifying Physician

__________ 7. Patient ID

__________ 8. Date of Birth

__________ 9. Race

__________ 10. Ethnicity

__________ 11. Gender

__________ 12. Country of Residence

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

Continued on next page
14. Method of Payment  
15. Any care at VA or Military Hospital?  
16. Calendar Base Date  
17. Randomization Date  
18. (Y/N) Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?  
19. (Y/N) Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?  
20. (Y/N) Have you obtained the patient's consent for his or her urine to be kept for use in research to learn about, prevent, treat, or cure cancer?  
21. (Y/N) Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?  
22. (Y/N) Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).  
23. (Y/N) Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?  
24. (Y/N) Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?
RTOG Institution #

RTOG 1010 ELIGIBILITY CHECKLIST—STEP 2 (HER2-positive patients only) (12/30/10)

Case # (page 1 of 2)

_______ (Y) 1. Is the patient's esophageal cancer HER2 positive by central testing?
_______ (Y) 2. Has the patient had surgical, medical oncology, and radiation oncology consultations per Section 3.1 of the protocol?
_______ (Y) 3. Were the history and physical exam with weight performed within the timeframes required in Section 3.1?
_______ (Y) 4. Were the whole-body PET/CT scan and endoscopic ultrasound performed within the timeframes required in Section 3.1?
_______(Y) 5. Was an EKG performed within 56 days prior to registration?
_______(Y) 6. Did the patient have a LVEF ≥ institutional lower limit of normal by cardiac echo or MUGA within 56 days prior to registration?
_______(Y) 7. Based on the PET scan and endoscopic ultrasound is the patient's clinical cancer stage, according to the AJCC 7th edition staging, either T1N1-2, T2-3N0-N2?
_______(N) 8. Does the patient have T1N0 disease, T4 disease, cervical esophageal carcinoma or proximal esophageal cancer?
_______(N) 9. Is there evidence of tracheoesophageal fistula or invasion into the trachea or major bronchi?
_______(Y) 10. Zubrod performance status 0-2?
_______(N) 11. Has the patient developed any of the comorbidities detailed in Section 3.2.12 since Step 1 registration?
_______(Y/NA) 12. For women of childbearing potential was a negative serum pregnancy test obtained within 14 days prior to Step 2 registration?
_______(Y) 13. Was serum creatinine ≤ 2 x upper limit of normal within 14 days prior to Step 2 registration?

The following questions will be asked at Study Registration for STEP 2:

3DCRT credentialing is required for this protocol

_______ 1. Institutional person randomizing case
_______(Y/N) 2. Is the patient going to receive protocol treatment?
   If no, provide reason:
   1. HER2 negative
   2. Does not meet eligibility requirements, specify: _________
   3. Physician preference
   4. Patient refusal
   5. Other complicating disease
   5. Other, specify: _________

Continued on next page

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3. Participant Initials (Last, First)
4. Verifying Physician
5. Patient ID
6. Calendar Base Date
7. Randomization Date
8. Has the Step 2 Eligibility Checklist been completed? (Y)
9. In the opinion of the investigator, is the patient eligible? (Y)
10. Medical Oncologist’s Name
11. Surgeon Name
12. Patient has consented to take part in the quality of life study? (Y/N)
   If no, provide reason:
   1. Patient refused due to illness
   2. Patient refused for other reason: specify ___________
   3. Not approved by institutional IRB
   4. Tool not available in patient’s language
   5. Other: specify_________________
13. Presence of adenopathy [(1) No or (2) Yes adenopathy, but celiac absent or (3) Yes adenopathy and celiac present ≤ 2 cm)]
14. Is the patient HER2 positive? (Y)

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 ______
1.0 INTRODUCTION

1.1 Trimodality Treatment of Esophageal Cancer

Neoadjuvant chemoradiation followed by esophagectomy has become a standard of care for esophageal cancer (Tepper 2008; Kleinberg 2007). Unfortunately, the majority of patients will relapse and die of their disease. Therapies that block aberrant growth factor pathways have substantial promise as a treatment for human malignancies, including esophageal cancer (Mendelsohn 1992; Makuda 1991). An important subset of patients with esophageal adenocarcinoma have HER2 overexpression (Safran 2007; Bang 2008; Grugan 2008; Brien 2000). Blocking this powerful growth factor signal may improve patient outcome.

1.2 The HER2 Gene

The HER receptor family consists of 4 transmembrane glycoproteins (HER1-HER4) (Makuda 1991). HER2 was the second member of the receptor family to be described. Structurally, HER2 is very closely related to HER1; however, it is inactivated more slowly than the other HER receptors, and its effects on cell proliferation and growth may last longer (Yarden 2001). No natural ligands are known to bind to HER2. Heterodimerization with other HER receptors and transactivation is the primary mode for initiating HER2 regulated signaling (Slamon 1987). HER2 is the preferred dimerization partner of the other HER family members (Vogel 2002).

The HER2 gene encodes a transmembrane glycoprotein receptor, p185HER2, that is targeted by the humanized anti-p185HER2 monoclonal antibody trastuzumab (Besalga 2005). Trastuzumab has received FDA approval for treatment of breast cancer. In the metastatic setting, trastuzumab increases survival in women with HER2-overexpressing breast cancer (Slamon 2001). In the adjuvant setting, trastuzumab dramatically reduces disease recurrence and increases survival for HER2-overexpressing breast adenocarcinoma (Romand 2005; Piccart-Gebhart 2005).

1.3 HER2 Expression in Esophageal Adenocarcinoma

Recent studies using modern, established techniques for quantifying HER2 expression demonstrate rates of HER2 overexpression in esophageal adenocarcinoma that are similar to breast cancer (Safran 2007; Bang 2008; Grugan 2008; Brien 2000). Brien et al (2000) reported HER2/neu gene amplification by fluorescence in situ hybridization (FISH) in 19% of patients, and this correlated with poor survival. Similar rates were reported by the Brown University Oncology Group (22% FISH+) [Safran 2007]. When HER2 positivity was defined as either FISH+ or immunohistochemistry (IHC) 3+, 33% of patients with distal esophageal adenocarcinoma overexpressed HER2 (Safran 2007).

The ToGA trial represents the largest phase III trial evaluating the potential role of trastuzumab in advanced gastroesophageal cancer. A total of 3807 patients were evaluated, representing the largest dataset to describe the extent of HER2-positive disease in advanced esophagogastric cancer (Bang 2008). Formalin-fixed, paraffin-embedded esophagogastric samples were centrally assayed by both modified HercepTest™ (IHC) and pharmDx (FISH) in parallel.

A score of IHC 3+ and/or FISH positive was defined as HER2 positive. The HER2 positivity was 22.1% for all patients with gastric and esophageal cancer. HER2 positivity was significantly associated with tumor location. The HER2 positivity was 19.9% for patients with gastric cancer. For patients with adenocarcinoma of the gastroesophageal junction and distal esophagus, the HER2 positivity rate was 32.2% in the ToGA trial.

1.4 Trastuzumab Increases Survival in HER2-Overexpressing Esophageal Cancer

The ToGA trial evaluated the addition of trastuzumab to cisplatin and a fluoropyrimidine (5-FU or capecitabine). Median overall survival was significantly improved with trastuzumab and chemotherapy as compared to chemotherapy alone, 13.5 versus 11.1 months, respectively [p = 0.0048, hazard ratio (HR) 0.74; 95% confidence interval (CI) 0.6-0.91] (Van Cutsem 2009). Overall response rate was 47.3% in patients receiving trastuzumab plus chemotherapy, as compared to 35.5% with chemotherapy alone (p = 0.0017). Safety profiles were similar, with no unexpected adverse events in the trastuzumab plus chemotherapy group. There was no difference in symptomatic congestive heart failure. Asymptomatic left ventricular ejection fraction (LVEF) decreases were reported in 4.6% of the trastuzumab-plus-chemotherapy group as compared to 1.1% of the chemotherapy group.
1.5 Selection of Paclitaxel/Carboplatin/Radiation for the Control Arm

There are many reasonable chemoradiation regimens in esophageal cancer (Herskovic 1992; Urba 2001; Minsky 1999; Walsh 1996; Kleinberg 2006; Bosset 1997; Burmeister 2005; Ilson 2009; Ku 2009, Kleinberg 2007). This protocol will utilize the regimen of weekly paclitaxel, carboplatin, and radiation following the report of the phase III trial by Gaast et al at ASCO 2010. This was a phase III study randomizing 363 patients to surgery alone versus trimodality therapy with paclitaxel, carboplatin, and concurrent radiation following by surgery. Major toxicities (grade ≥ 3) in the chemoradiation arm included leukopenia in 7% of patients. Nonhematologic toxicities were all below 5%. The reported R0 resection rate was 92.3% in the chemoradiation arm versus 64.9% in the surgery alone arm. In 132 resected specimens receiving trimodality treatment, the pathologic complete response rate was 32.6%. In-hospital mortality was 3.7% in the surgery alone arm versus 3.8% in the chemoradiation arm. With a median follow-up of 32 months, 70 and 97 patients had died in the chemoradiation group versus surgery alone group, respectively. The overall survival was significantly better (p = 0.011) in the group of patients treated with chemoradiation (HR 0.67 [95% CI 0.50-0.92]). Median survival was 49 months in the chemoradiation arm versus 26 months in the surgery alone arm. Survival rates of 1, 2, and 3 years are 82%, 67% and 59% in the chemoradiation arm and 70%, 52% and 48% in the surgery alone arm.

The protocol will utilize the standard preoperative radiation dose of 50.4 Gy used in the pilot study of trastuzumab with chemoradiation (Safran 2007) and phase III United States preoperative esophageal cancer studies (Tepper 2008).

1.6 Decision to Include Esophageal Tumors That Are FISH+ and/or IHC 3+

Subset analysis in the ToGA trial suggested that patients with HER2-positive esophageal cancer who benefitted most were those with tumors that were 3+ IHC positive; patients with tumors that were FISH+ but had weak IHC staining did not benefit. However, in breast cancer, it has been strongly established that all FISH+ patients may benefit from adjuvant trastuzumab, with an approximate 50% reduction in recurrence. It is possible that interpretation of IHC in esophageal cancer may have been different as compared to previous breast cancer studies. This study will use centralized testing by IHC and FISH for HER2 positivity and will include all patients that are FISH+ or IHC 3+, since this previously has been established as beneficial in the adjuvant setting for patients with HER2-positive breast cancer.

1.7 Maintenance Trastuzumab

Maintenance trastuzumab will be administered for approximately 1 year based on data from 4 seminal adjuvant breast cancer trials: the National Surgical Adjuvant Breast and Bowel Project Trial (NSABP) B-31; the North Central Cancer Treatment Group (NCCTG) study N-9831; the HERA trial; and the BCIRG 006 (Romand 2005; Piccart-Gebhart 2005; Perez 2007; Smith 2007; Untch 2008; Slamon 2006; Mackey 2009; Robert 2007). NSABP B-31 and N-9831 were initially designed as separate trials comparing doxorubicin plus cyclophosphamide followed by paclitaxel with and without 1 year of adjuvant trastuzumab. In the latest combined analysis, there was a 49% reduction in the risk of disease recurrence trastuzumab (4-year disease-free survival 86% versus 73% percent; HR 0.51), and a 37% reduction in the risk of death (4-year overall survival 93% versus 89%; HR 0.63) (Perez 2007).

The HERA trial, in which 5090 women received standard chemotherapy with or without 1 or 2 years of adjuvant trastuzumab had similar findings following 1 year of trastuzumab. There was a 36% reduction in disease recurrence as well as an improvement in overall survival (Piccart-Gebhart 2005; Smith 2007; Untch 2008). Data have not been reported for the 2-year group. The BCIRG 006 trial evaluated the efficacy of 2 anthracycline containing regimens (AC followed by docetaxel) to a non-anthracycline containing regimen (carboplatin and docetaxel) with and without 1 year of adjuvant trastuzumab (Slamon 2006; Mackey 2009; Robert 2007). In an initial analysis, the disease-free survival favored the trastuzumab-containing regimens and the safety profile favored TCH [Taxotere (docetaxel)/carboplatin/Herceptin (trastuzumab)]. There were fewer symptomatic cardiac events and a lower incidence of asymptomatic decline in LVEF with TCH compared to either anthracycline group. Furthermore, there were 4 leukemias in the anthracycline-containing arms versus none in the TCH-treated women.
All of the previously described trials studied at least 1 year of adjuvant trastuzumab. Almost 10,000 patients with HER2-positive breast cancer are included in these 4 trials. The FINHER trial evaluated the use of 9 weekly trastuzumab treatments after chemotherapy (Joensuu 2006; Joensuu 2009). In this trial, which included 232 patients with HER2-positive breast cancer, a benefit of trastuzumab was demonstrated. However, it is not known whether short-course trastuzumab would have the same benefit as 1 year of maintenance treatment.

1.8 Issues Related to Cardiac Toxicity
In the 4 large adjuvant breast cancer trastuzumab trials (NSABP B32, N-9831, HERA, and BCIRG), the incidence of severe heart failure (NYHA class III/IV) has ranged from 0.6% to 4.1%, while the incidence of an asymptomatic decrease in LVEF was between 7.4% and 17.3% (Telli 2007; Tan-Chiu 2005). Risk factors for cardiotoxicity included the use of anthracyclines, advanced age, and a previous risk of cardiac disease. In the proposed adjuvant esophageal cancer trial, patients will not receive an anthracycline, and all patients will be required to have a normal pretreatment LVEF (Perez 2004). Any patient with a history of heart failure will be excluded from this study.

Current evidence suggests that the risk of radiation with concurrent trastuzumab does not substantially increase the risk of cardiac dysfunction. Halyard et al (2009) retrospectively examined adverse events data from the NCCTG phase III trial, N9831, and directly evaluated the effect of trastuzumab on radiation-induced cardiac toxicity. At a median follow up of 3.7 years, radiotherapy concurrently with trastuzumab did not increase relative frequency of cardiac events, regardless of treatment side, suggesting that concurrent adjuvant radiation therapy and trastuzumab was not associated with increased acute adverse events.

To carefully monitor for cardiac toxicity, all patients will be required to have physical examinations at least every 6 weeks while on maintenance trastuzumab. Furthermore, determination of LVEF will be performed at completion of chemoradiation, then at month 3, 6, 9 and 12. A standard dose modification scheme, which has been applied to adjuvant trastuzumab in breast cancer, will be utilized in this study.

1.9 Preliminary Data: Trastuzumab with Chemoradiation for Esophageal Cancer
The Brown University Oncology Group performed a pilot trial evaluating the addition of trastuzumab to chemoradiation for patients with locally advanced, HER2-overexpressing, esophageal adenocarcinoma (Safran 2004; Safran 2007). The goals of this study were to establish the safety of trastuzumab both with chemoradiation and continued for 1 year as maintenance. Secondary goals were to obtain preliminary survival data. Patients with adenocarcinoma of the esophagus without distant organ metastases and 2+/3+ HER2 overexpression by IHC were eligible. FISH was performed to determine HER2 gene copy number on tumor tissue from all patients.

All patients received cisplatin, 25 mg/m², and paclitaxel, 50 mg/m², weekly for 6 weeks with radiation, 50.4 Gy. The first and second cohorts of 3 patients received trastuzumab, 2 mg/kg, and 3 mg/kg bolus followed by weekly x 5 week dosing of 1 mg/kg and 1.5 mg/kg with chemoradiation. The final 13 patients received trastuzumab, 4 mg/kg, on week 1, followed by 2mg/kg for 5 weeks. Maintenance trastuzumab was 6 mg/kg every 21 days for a total of 1 year of trastuzumab. Attempted surgical resection was not required if patients had medical comorbidities or distant adenopathy that precluded surgery. Echocardiogram was performed every 4 months. Nineteen patients were entered; 7 (37%) had celiac adenopathy and 7 (37%) had retroperitoneal, portal adenopathy or scalene adenopathy.

There were no increases in adverse events from the addition of trastuzumab. Acute toxicities for all patients are listed in the table below. Multiple toxicities in the same patient are scored as separate events. There was only 1 incidence of grade 4 esophagitis and 1 of grade 3 esophagitis. There were no cardiac toxicities. Prophylactic feeding tubes were not used. Other grade 3/4 adverse events included nausea (3), dehydration (1), neutropenia (4), hypersensitivity to paclitaxel (1), and infection (1). There were no complications from maintenance treatment.
Highest Adverse Event Grade for Each Patient (N=19)

<table>
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<tr>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0</td>
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</table>

The 3-year survival of all 19 patients was 47%, which includes patients not candidates for surgical resection due to medical comorbidities or distant adenopathy.

1.10 **Esophageal Cancer Related Quality of Life**

The quality of survival, in addition to the length of survival, is now accepted by oncologists as an important clinical endpoint in phase III trial design for patients with locally advanced cancers (Burris 1997; ASCO 1996). To date, there has been limited available literature using formal health-related quality of life (QOL) measures for patients with esophageal cancer receiving definitive chemoradiation on prospective trials. However, RTOG has evaluated QOL for patients with localized esophageal cancer on a large randomized phase III effort (Kachnic 2001). RTOG 94-05 (Intergroup 0123) compared the QOL outcomes for patients with esophageal cancer receiving chemoradiation with conventional dose radiation (50.4 Gy) versus high-dose radiation (64.8 Gy). QOL was assessed using the Functional Assessment of Cancer Therapy (FACT) Head & Neck (version 2) (Cella 1993) at baseline, after chemoradiation, at 8 months after therapy, and at 1 year. Two-year outcome analysis showed no survival or local control benefit for the 64.8 Gy arm (Kachnic 2001). In terms of QOL, functional and swallowing scores were decreased after chemoradiation in both treatment arms, with total QOL scores significantly poorer than baseline in the 64.8 Gy arm.

One factor associated with the paucity of QOL data to assess treatment efficacy for esophageal cancer has been the lack of a validated QOL instrument tailored to this patient population. More recently, the FACT-Esophageal (FACT-E) questionnaire has been developed, used prospectively (Brooks 2002), and undergone validation (Darling 2006) for adult patients with esophageal cancer.

Scores on the FACT-E correlate well with several important clinical factors and were found to be responsive to change in patients treated with esophagectomy alone and in those treated with neoadjuvant chemoradiotherapy (Darling 2006).

In trimodality therapy for locally advanced esophageal cancer, it is difficult to predict which patients will benefit from surgical resection following neoadjuvant chemoradiation. To this end, several methods to predict response to neoadjuvant chemoradiation are under investigation. Repeated computed tomography scanning, endoscopy, and endoscopic ultrasound have not been particularly helpful in predicting early response to chemoradiation therapy (Beseth 2000; Swisher 2004). The use of therapy-induced metabolic changes in the tumor glucose metabolism by positron emission tomography (PET) has shown some reliability in adenocarcinoma of the gastroesophageal junction (Ott 2006; Weber 2001). Yet, this method has not shown enough accuracy at predicting nonresponders in squamous cell carcinoma or in patients receiving chemoradiation. An improvement of the leading symptoms (in this case, dysphagia) early in the treatment course also may prove useful as a predictor of chemoradiation response (Darling 2006). In patients treated with neoadjuvant chemoradiotherapy, a significant improvement was reported in the esophageal cancer swallowing subscale (Swallowing Index Subscale Score) and eating subscale (Eating Index Subscale Score) of the FACT-E at 6 to 8 weeks following chemoradiation (Darling 2006). It is therefore hypothesized, for the primary QOL question in this study, that an improvement in patient-reported QOL (specifically, the Esophageal Cancer Subscale, or ECS, of the FACT-E) at 6 weeks post-completion of neoadjuvant chemoradiation is predictive of pathologic complete response.
The Functional Assessment of Cancer Therapy-Esophageal (FACT-E)

This QOL instrument has been specifically designed for adults with esophageal cancer. The FACT-E questionnaire has been used prospectively (Brooks 2002) and undergone validation (Darling 2006). The FACT-E self-reporting scale is comprised of the validated FACT-General core (27 general items including the 4 domains of physical well-being, social and family well-being, emotional well-being, and functional well-being, which had been developed for adults with various cancer diagnosis) (Cella 1993; Overcash 2001), combined with the new FACT-E subscale (the ECS), which includes 17 additional items specific for symptoms and problems related to esophageal cancer, such as eating, appetite, swallowing, pain, talking/communicating, mouth dryness, breathing difficulty, coughing, and weight loss. The total FACT-E score is the sum of the esophageal-specific questions and the FACT-G scores.

Each FACT-E question has a possible 5-point response of 0-4 (i.e., not at all to very much). Negatively worded items are reverse scored so that higher scores always represent better QOL or less severe symptoms. The total questionnaire takes the patient approximately 10 minutes to complete. As with the FACT-G, higher scores indicate a better health-related QOL or functioning. The FACT-E 44-item questionnaire has undergone psychometric testing in patients with esophageal cancer (Darling 2006). The FACT-E had good construct validity (convergence and divergence) when compared with the EORTC QLQ 30 and its specific esophageal module. It had very good to excellent internal consistency and reliability. FACT-E scores correlated well with several important clinical factors and were found to be responsive to change in patients treated with esophagectomy alone and in those treated with neoadjuvant chemoradiotherapy. In the subset of patients treated with neoadjuvant chemoradiotherapy, a significant improvement was reported in the ECS swallowing subscale (Swallowing Index Subscale Score) and eating subscale (Eating Index Subscale Score) at 6 to 8 weeks following chemoradiation (Darling 2006). The FACT-E, version 4, will be used to measure QOL, with the focus on the ECS. Patients will complete the FACT-E at the following time points: pretreatment (baseline), 6 weeks following chemoradiation plus trastuzumab at the time of restaging prior to surgical resection, at 1 year from the start of treatment, and at 2 years from the start of treatment.

There are no published data to date demonstrating how QOL is affected by the addition of trastuzumab to standard chemoradiation regimens for the treatment of gastrointestinal malignancies. Based on the impressive local response rates associated with the use of trastuzumab and on data from Darling and colleagues (2006), we also hypothesize that the addition of trastuzumab to standard chemoradiation for HER2-positive locally advanced esophageal cancer will improve the FACT-E ECS score by at least 5 points. Further QOL endpoints will determine if the addition of trastuzumab to standard chemoradiation improves the Swallowing Index Subscale Score and the Eating Index Subscale Score of the FACT-E ECS by at least 2 points and if pathologic complete response correlates with the ECS Score at 1 year and/or 2 years from the start of treatment.

The EuroQol (EQ-5D)

Patient-reported outcomes (PROs) are increasingly being incorporated into clinical trials for documentation of effects of treatment not measured by traditional endpoints, such as overall and disease-free survival (Safran 2008). This is important with interventions that may increase treatment-related side effects without positively impacting survival. Quality-adjusted survival is an endpoint that incorporates a patient’s utility or preference of the health state that is combined with the time spent in that health state. The resultant is a quality-adjusted life-year (QALY). Utility can be measured by different methods including Standard Gamble, Time Trade-Off, and Health Utilities Index III. The EuroQol (EQ-5D) is another instrument for measuring utilities. It is a 2-part questionnaire that takes the patient approximately 5 minutes to complete (Schulz 2002). The first part consists of 5 items covering 5 dimensions, including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problem, 2-moderate problems, and 3-extreme problems. There are 243 potential health states. The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm, 10 point-interval scale. Either the index score or the VAS score can be used in the quality-adjusted survival analysis (Wu 2002). The benefit of measuring quality-adjusted survival is that the product, quality-adjusted survival, can be compared to the outcomes of other interventions across disease sites and can be used by health policy makers to rank interventions.
The EQ-5D has been used to evaluate interventions in patients with esophageal cancer. Williams et al (2006) found a baseline utility of .676 and .663 in patients undergoing esophageal endoscopy by a physician and nurse, respectively, in the Multi-Institution Nurse Endoscopy Trial (MINuET). A utility is a patient preference for a certain health state, with 0 being death and 1 being perfect health. There are some health states with a utility of < 1. At 1 year, patient utility increased to .725 and .703 for endoscopy by a physician and nurse, respectively. Jones et al (2003) used the EQ-5D to assess heartburn in patients with gastroesophageal reflux disease in Germany and Sweden. They found a reduction in health-related QOL in patients with heartburn, with patients with more severe heartburn symptoms having reduced quality-adjusted survival. Of note, they did not find a relationship between the findings at endoscopy and the severity of symptoms as measured by the Gastrointestinal Symptom Rating Scale (GSRS) or the EQ-5D.

The EQ-5D will be used to assess quality-adjusted survival. Protocol-eligible patients will be included in the quality-adjusted survival analysis only if they have provided baseline and at least 1 subsequent measurement. Patients will complete the EQ-5D at the following time points: pretreatment (baseline), at 1 year from the start of treatment, and at 2 years from the start of treatment. Quality-adjusted survival is then calculated as the weighted sum of different time in different health states added up to a total quality-adjusted survival time \[U = \text{sum of quality (qi) of health states K times the duration (si) spent in each health state)}\] (Glasziou 1990).

The FACT-E and EQ-5D questionnaires are being completed in the currently active phase III study, RTOG 0436, evaluating the addition of cetuximab to non-operative treatment of esophageal cancer in patients.

For this trial, all protocol eligible-patients (those that are HER2 positive) will be asked to participate in the QOL component of this study. In this study, as well as other RTOG studies, baseline QOL is not mandated as part of the pretreatment evaluation. RTOG feels that this allows patients who want to participate in a clinical trial, but who do not want to participate in the QOL portion, to still have access to the trial and its potential benefits. However, we have found that on our ongoing RTOG 0436 study, 91% of all eligible patients consented to baseline QOL, and of these, 93% participated in baseline FACT-E and EQ-5D assessments.

Patients will be included in the QOL analysis only if they have provided both baseline and at least 1 subsequent measurement. This is done because of the attrition of QOL completion over time, a challenge that affects the majority of QOL studies. We have found on RTOG 0436, that at 6 to 8 weeks following chemoradiation, QOL participation was 65.5% and 62% for FACT-E and EQ-5D, respectively; no participation was reported in 12.7% and 13.9% for FACT-E and EQ-5D, respectively; and completed assessments have not yet been received by RTOG Headquarters in 21.8% and 24.2% for FACT-E and EQ-5D, respectively. This attrition is demonstrated despite robust efforts on the part of RTOG to minimize missing data. As such, due to the potential attrition of QOL participation all HER2-eligible patients will be allowed to consent to QOL in this trial.

1.11 Summary of Study Rationale

HER2 is fundamentally overexpressed, as measured by gene amplification by FISH and IHC, in a similar rate in esophageal and breast adenocarcinoma. In North America, HER2-expressing esophageal adenocarcinoma is associated with advanced locoregional adenopathy and a poor prognosis. Trastuzumab increases survival in metastatic breast cancer that overexpresses HER2 and dramatically reduces recurrence and increases survival in adjuvant breast cancer. Similarly, a large international phase III trial demonstrates that trastuzumab increases survival in metastatic gastroesophageal cancer. Neoadjuvant trastuzumab combined with chemoradiation followed by maintenance chemotherapy is safe in esophageal cancer. A phase III trial evaluating the addition of trastuzumab to trimodality treatment of esophageal cancer will be performed to determine if trastuzumab increases disease-free and overall survival and improves quality-adjusted survival for patients with HER2-overexpressing esophageal adenocarcinoma.
2.0 OBJECTIVES

2.1 Primary Objective
2.1.1 To determine if trastuzumab increases disease-free survival when combined with trimodality treatment (radiation plus chemotherapy followed by surgery) for patients with HER2-overexpressing esophageal adenocarcinoma

2.2 Secondary Objectives
2.2.1 To evaluate if the addition of trastuzumab to trimodality treatment increases the pathologic complete response rate and overall survival for patients with HER2-overexpressing esophageal adenocarcinoma;
2.2.2 To develop a tissue bank of tumor tissue from patients with non-metastatic esophageal adenocarcinoma;
2.2.3 To determine molecular correlates of complete pathologic response, disease-free survival, and overall survival for patients with HER2-overexpressing esophageal adenocarcinoma treated with neoadjuvant and maintenance trastuzumab;
2.2.4 To evaluate predictors of cardiotoxicity in patients with esophageal cancer treated with trastuzumab and chemoradiation;
2.2.5 To evaluate adverse events associated with the addition of trastuzumab to trimodality treatment for patients with non-metastatic esophageal adenocarcinoma;
2.2.6 Patient-Reported Quality of Life Objectives
2.2.6.1 To determine if the addition of trastuzumab to trimodality treatment improves the patient-reported Functional Assessment of Cancer Therapy for Esophageal Cancer (FACT-E) Esophageal Cancer Subscale (ECS) score;
2.2.6.2 To determine if an improvement in the FACT-E ECS score at 6-8 weeks post completion of neoadjuvant chemoradiation correlates with pathologic complete response;
2.2.6.3 To determine if pathologic complete response correlates with the FACT-E ECS score at 1 year and/or 2 years from the start of chemoradiation;
2.2.6.4 To determine if the addition of trastuzumab to trimodality treatment improves the Swallow Index and Eating Index Subscale scores of the FACT-E;
2.2.6.5 To determine if the addition of trastuzumab to paclitaxel, carboplatin, and radiation impacts quality-adjusted survival.

3.0 PATIENT SELECTION

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

3.1 Conditions for Patient Eligibility
3.1.1 Conditions for Patient Eligibility PRIOR TO STEP 1 REGISTRATION BUT WITHIN 56 DAYS PRIOR TO STEP 2 REGISTRATION
3.1.1.1 Pathologically confirmed primary adenocarcinoma of the esophagus that involves the mid (up to 25 cm), distal, or esophagogastric junction. The cancer may involve the stomach up to 5 cm
3.1.1.2 Endoscopy with biopsy
3.1.1.3 Intent to submit tissue for central HER2 testing per section 10.2.3
3.1.1.4 Stage T1N1-2, T2-3N0-2, according to the American Joint Committee on Cancer (AJCC) 7th edition staging, based upon the following minimum diagnostic work-up:
   ▪ Chest/abdominal/pelvic CT or whole-body PET/CT (NOTE: if CT is performed at this time point whole-body PET/CT will be required prior to Step 2 registration)
   ▪ Patients may have regional adenopathy including para-esophageal, gastric, gastrohepatic and celiac nodes. If celiac adenopathy is present, it must be ≤ 2 cm.
   ▪ Patients with tumors at the level of the carina or above must undergo bronchoscopy to exclude fistula
3.1.1.5 Age ≥ 18
3.1.1.6 Zubrod performance status 0-2
3.1.1.7 CBC/differential obtained, with adequate bone marrow function defined as follows:
   ▪ Absolute neutrophil count (ANC) ≥ 1,500 cells/mm³
   ▪ Platelets ≥ 100,000 cells/mm³
   ▪ Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)
3.1.1.8 Additional laboratory studies
- Creatinine ≤ 2 x the upper limit of normal
- Bilirubin ≤ 1.5 x upper limit of normal
- AST ≤ 3 x upper limit of normal
- For women of childbearing potential, a negative serum or urine pregnancy test

3.1.1.9 Patients must sign study-specific informed consent prior to study entry

3.1.2 Conditions for Patient Eligibility **PRIOR TO STEP 2 REGISTRATION (HER2-positive patients only)**

3.1.2.1 HER2 expressing adenocarcinoma of the esophagus centrally assessed within 56 days prior to Step 2 registration

3.1.2.2 Surgical consultation to confirm that patient will be able to undergo curative resection after completion of chemoradiation within 56 days prior to Step 2 registration

3.1.2.3 Radiation oncology consultation to confirm that disease can be encompassed in a radiotherapy field within 56 days prior to Step 2 registration

3.1.2.4 Consultation with a medical oncologist within 56 days prior to Step 2 registration

3.1.2.5 Stage T1N1-2, T2-3N0-2, according to the AJCC 7th edition staging, based upon the following minimum diagnostic work-up:

3.1.2.5.1 History/physical examination, with documentation of the patient’s weight, within 14 days prior to Step 2 registration

3.1.2.5.2 Endoscopic ultrasound within 56 days prior to Step 2 registration (if only CT performed prior to Step 1 registration)

3.1.2.5.3 EKG within 56 days prior to Step 2 registration

3.1.2.5.4 Serum creatinine ≤ 2 x the upper limit of normal within 14 days prior to step 2 registration

3.1.2.6 Zubrod performance status 0-2 within 14 days prior to Step 2 registration

3.1.2.7 For women of childbearing potential, a negative serum pregnancy test within 14 days prior to Step 2 registration

3.1.2.8 LVEF ≥ institutional lower limit of normal by cardiac echo or MUGA scan within 56 days prior to Step 2 registration

3.1.2.9 Women of childbearing potential and sexually active male participants must agree to practice adequate contraception while on study and for at least 60 days following the last dose of chemotherapy or trastuzumab

3.2 Conditions for Patient Ineligibility

3.2.1 Patients with cervical esophageal carcinoma

3.2.2 Patients with T1N0 disease, T4 disease, and proximal esophageal cancers (15-24 cm)

3.2.3 Prior systemic chemotherapy for esophageal cancer; note that prior chemotherapy for a different cancer is allowable

3.2.4 Prior radiation for esophageal cancer or prior chest radiotherapy

3.2.5 Prior anthracycline or taxane

3.2.6 Evidence of tracheoesophageal fistula or invasion into the trachea or major bronchi

3.2.7 Prior invasive malignancy (except non-melanomatous skin cancer), unless disease free for a minimum of 2 years (e.g., carcinoma in situ of the breast, oral cavity, or cervix are permissible)

3.2.8 Medical contraindications to esophagectomy

3.2.9 Prior therapy with any agent targeting the HER2 pathway or HER1 (EGFR)pathway

3.2.10 Prior therapy with trastuzumab

3.2.11 Prior allergic reaction to the study drugs involved in this protocol or to a monoclonal antibody

3.2.12 Previous history of congestive heart failure

3.2.13 Severe, active comorbidity, defined as follows:

3.2.13.1 Unstable angina in the last 6 months

3.2.13.2 Transmural myocardial infarction within the last 6 months

3.2.13.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.2.13.4 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 in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.
3.2.14 Pregnant or nursing women or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management
4.1.1 PFTs (including routine spirometry and DLCO) within 56 days prior to Step 2 registration
4.1.2 Na, K, BUN, glucose within 14 days prior to Step 1 registration and again 14 days prior to Step 2 registration

4.2 Strongly Recommended Evaluations/Management
4.2.1 Arterial blood gas within 56 days prior to Step 2 registration

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements for 3D-CRT Treatment Approach
5.1.1 Only institutions that have met the technology requirements and that have provided the baseline physics information may enter patients onto this study.
5.1.2 The Facility Questionnaire (one per institution, available on the ATC web site at http://atc.wustl.edu) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

5.2 Regulatory Pre-Registration Requirements
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=CTSU-IRBCertifForm.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.

5.3 Summary of Patient Registration Procedures
Once the site has met pre-registration requirements, this study incorporates a 2-step registration process.

Step 1 of registration entails an initial registration for HER2 testing and to document that the patient meets Step 1 eligibility criteria (See Section 3.1.1).
   - The site will register the patient and will then submit tissue for HER2 testing per Section 10.2.

Step 2 of registration entails a second web registration, after which the patient will either be randomized to treatment or it will be documented that the patient will not receive protocol treatment.
If the patient is determined to be HER2 negative, the site will not proceed to Step 2 registration.

If the patient is determined to be HER2 positive and the patient will not receive protocol treatment for any reason, the site will proceed to Step 2 registration to document the reason. The patient will not be randomized.

If the patient is determined to be HER2 positive and the patient will receive protocol treatment, the site will proceed to Step 2 registration and the patient will be randomized to Arm 1 or Arm 2.

See Section 5.4 for online registration procedures.

5.4 Registration
5.4.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user 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 and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form at 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 (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.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org or 800-227-5463 ext. 4189 or 215-574-3189

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. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) Is Not Allowed.

Radiation therapy must begin within 10 days after STEP 2 registration, on a Monday or Tuesday if possible.
6.1 Dose Specifications

NOTE: ICRU-50 and ICRU-62 prescription methods and nomenclature shall be utilized for this study.

6.1.1 The prescription volume is the PTV. The dose to the ICRU reference point at the isocenter will be reported. Dose is specified in cGy to muscle.

6.1.2 Tissue Heterogeneity
CT-based treatment planning is required. Calculations that take into account tissue heterogeneity shall be used. Acceptable calculation algorithms such as the superposition/convolution and not pencil-beam or Clarkson algorithms should be used.

6.1.3 The total dose for both arms will be 50.4 Gy in 28 fractions. The initial phase will be 45 Gy in 25 fractions. A minimum of 95% of the planning target volume (PTV) will receive 45 Gy. No more than 10% of the PTV shall receive greater than 50 Gy. The final boost will be for an additional 5.4 Gy in 3 fractions. For this phase, a minimum of 95% of the boost PTV will receive 5.4 Gy. No more than 10% of the boost PTV will receive more than 6 Gy for the boost phase.

6.2 Technical Factors

Megavoltage equipment with effective photon energies ≥ 6MV is required.

6.3 Localization, Simulation, and Immobilization

6.3.1 CT-based treatment planning is required for this study. The planning CT should encompass the entire thoracic cavity and the abdomen to a level below the bottom of the kidneys. A minimum slice thickness of 3-5 mm is required through regions of the gross tumor volume (GTV) and a minimum of 8-10 mm is required elsewhere. A uniform 5 mm thickness may be utilized.

6.3.2 The patient is to be positioned in an individualized immobilization device in the treatment position on a flat hard table. The patient may be in the supine or prone position.

6.3.3 Esophageal contrast may be used during simulation but is optional if a diagnostic CT scan with contrast was performed.

6.4 Treatment Planning/Target Volumes

6.4.1 ICRU-50 and ICRU-62 prescription and nomenclature shall be utilized for this study. All available information shall be utilized to define target volumes including endoscopic ultrasound, esophagram, CT or other imaging findings including PET/CT.

6.4.2 Gross Tumor Volume (GTV)
The GTVp is defined as the primary tumor in the esophagus. The GTVn is defined as any grossly involved regional lymph nodes.

6.4.3 Clinical Target Volume (CTV)
The CTV is defined as the GTVp with a 4 cm expansion superiorly and inferiorly along the length of the esophagus and cardia and a 1.0-1.5 radial expansion plus the GTVn with a 1.0-1.5 expansion in all dimensions. This volume should be expanded if needed to cover the paraesophageal and celiac lymph node regions. The 4 cm superior and inferior expansion should follow the contour of the esophagus and proximal stomach. The intent is to extend the margin along the length of the esophagus and proximal stomach to provide a margin for coverage of submucosal extension of tumor. The celiac axis should be covered for tumors of the distal esophagus or gastroesophageal junction.

6.4.4 Planning Target Volume (PTV)
Additional margin shall be added to the CTV for setup error and movement. This expansion should be 0.5 to 1.0 cm and does not need to be uniform in all dimensions. 4DCT data is allowed to customize PTV expansion.

6.4.5 Boost PTV
The boost PTV is defined as the GTVp along the length of the esophagus and GTVn with an expansion of 0.5 to 1.0 cm. The expansion does not need to be uniform in all dimensions. 4D-CT data is allowed to customize PTV expansion.

6.5 Critical Structures

6.5.1 Organs at risk to be contoured include both lungs, kidneys, heart, and spinal cord. The left ventricle should also be contoured. A contrast-enhanced CT scan should be available for contouring the left ventricle.

6.5.2 Spinal cord maximum dose must not exceed 45 Gy.
6.5.3 At least 60% of the liver must receive $\leq 30$ Gy and the mean liver dose must be less than 25 Gy.
6.5.4 At least 70% of the combined kidney volume should be kept below 20 Gy. If there is only one functioning kidney, 80% must receive $\leq 20$ Gy.
6.5.5 The entire heart should receive less than 30 Gy and 50% of the heart should receive less than 40 Gy. There is no separate left ventricle constraint.
6.5.6 Lung tissue more than 2 cm outside the target volume must not receive more than 40 Gy. The total lung volume receiving 30 Gy must be less than 20%. The lung volume receiving more than 20 Gy must be less than 30% and ideally will be less than 25%. The volume of lung receiving more than 10 Gy should be less than 40%, the volume of lung receiving greater than 5 Gy less than 60% and the mean lung dose less than 20 Gy.
6.5.7 Multiple shaped fields should be utilized to meet the target volume and normal tissue constraints.

6.6 Documentation Requirements
First day port films or portal images of each field must be obtained and kept by the treating institution and must be available for review upon request. Twice weekly (at least 48 hours apart) verification films or images of orthogonal views (anterior to posterior and lateral projection) must be reviewed by the treating physician. Daily image guidance is encouraged but not required. If daily image guidance is utilized, it must be documented.

6.7 Compliance Criteria
Not more than 10% of the PTV shall receive a dose in excess of 50 Gy. The maximum point dose to lung tissue more than 2 cm outside the PTV shall not exceed 40 Gy. The lung volume receiving 20 Gy must be below 30%. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure. When all constraints are met, the physician is encouraged to reduce lung dose as much as possible.

6.8 R.T. Quality Assurance Reviews
One of the Radiation Oncology Co-Chairs, Dr. Ted Hong, Dr. Michael Haddock, or Dr. Thomas Dipetrillo, will perform an RT Quality Assurance Review after complete RT data is received. These reviews will be ongoing.

6.9 Elapsed Days/Therapy Interruptions
6.9.1 Elapsed Days
- **Per Protocol:** 25 – 32 total elapsed days
- **Variation Acceptable:** 33 – 39 total elapsed days
- **Deviation Unacceptable:** $\geq$ 40 total elapsed days

6.9.2 Therapy Interruptions
Interruption of radiation is permitted only on the basis of toxicity. When radiation is interrupted for toxicity, systemic therapy with paclitaxel, carboplatin, and trastuzumab also should be interrupted. Therapy will be interrupted for absolute granulocyte counts $\leq$ 500; platelet count $\leq$ 50,000; and $\geq$ grade 3 radiation-related, non-hematologic toxicity. If the patient develops $\geq$ grade 3 radiation-related toxicity, radiation therapy and chemotherapy should be withheld. Interruption of therapy may continue until the toxicity has regressed to $\leq$ grade 2 to allow resumption of therapy; however, every effort should be made to limit treatment interruptions to 1-2 weeks. If a patient develops grade 3 esophagitis in the last week of treatment, radiation therapy and trastuzumab (but not chemotherapy) may continue at the discretion of the treating physician.

6.9.2.1 Dose Modifications
Every effort must be made to deliver the full 50.4 Gy to all patients. Toxicity may be encountered that is sufficiently severe to require treatment interruption. Once the toxicity has resolved, the patient’s therapy should resume and full protocol radiation dose should be delivered. The toxicity that forced any dose reduction must be documented. Total number of fractions and elapsed days should be carefully reported. If an interruption of more than 2 weeks is necessary, resumption of treatment is at the discretion of the radiation oncology chairs. The patient’s treatment plan will be considered a major deviation, but follow up will be continued.
6.10 Radiation Adverse Events
Adverse effects related to radiation therapy include nausea/vomiting, diarrhea, weight loss, fatigue, myelosuppression, skin erythema, subcutaneous fibrosis, esophagitis, carditis, myelitis, acute radiation pneumonitis and late pulmonary fibrosis, and esophageal stricture.

6.11 Radiation Adverse Event Reporting
See Section 7.8.

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.

Protocol treatment must begin within 10 days after STEP 2 registration.

7.1 Treatment
7.1.1 Arm 1: Trastuzumab, Paclitaxel, and Carboplatin with Concurrent Radiation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose*</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>4 mg/kg IV Day 1</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2 mg/kg IV Day 8, 15, 22, 29, 36</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>6 mg/kg IV On day 57</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>50 mg/m² IV Day 1, 8, 15, 22, 29, 36</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC = 2 Day 1, 8, 15, 22, 29, 36</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>50.4 Gy, at 180 cGy/fx Day 1-5, 8-12, 15-19, 22-26, 29-33, 36-38</td>
<td></td>
</tr>
</tbody>
</table>

Maintenance trastuzumab 6 mg/kg IV Once every 3 weeks x 13 treatments beginning as soon as the patient has recovered from surgery, at a minimum of 21 days and a maximum of 56 days

*Based on actual body weight.

7.1.2 Arm 2: Paclitaxel and Carboplatin with Concurrent Radiation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose*</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>50 mg/m² IV Day 1, 8, 15, 22, 29, 36</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC = 2 Day 1, 8, 15, 22, 29, 36</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>50.4 Gy, at 180 cGy/fx Day 1-5, 8-12, 15-19, 22-26, 29-33, 36-38</td>
<td></td>
</tr>
</tbody>
</table>

*Based on actual body weight.

7.2 Details of Chemotherapy
7.2.1 Trastuzumab
Trastuzumab will be administered prior to paclitaxel and carboplatin. The initial dose of trastuzumab is 4 mg/kg intravenously administered over 90 minutes on day 1, followed by weekly infusions of 2 mg/kg intravenously over 30-60 minutes on days 8, 15, 22, 29, and 36. Trastuzumab, 6 mg/kg IV will be given on day 57. As soon as the patient has recovered from surgery, at a minimum of 21 days and a maximum of 56 days, patients will receive trastuzumab, 6 mg/kg IV once every 3 weeks, over 30-90 minutes x 13 doses.

7.2.2 Paclitaxel
Paclitaxel 50 mg/m² will be administered as an intravenous infusion over 1 hour on days 1, 8, 15, 22, 29, and 36.

Prior to the first dosage of paclitaxel, patients will be premedicated with dexamethasone 20 mg orally the night before and 20 mg either orally or intravenously on the morning of paclitaxel administration. On the morning of the first paclitaxel administration: if dexamethasone is given intravenously, administer 30 minutes prior to paclitaxel administration; if dexamethasone is given orally, administer 1-3 hours prior to paclitaxel administration. Also prior to the first dosage
of paclitaxel, patients will be premedicated with diphenhydramine, 50 mg intravenously, and ranitidine (or other H2 blocker), 50 mg intravenously. If no allergic reactions occur, then subsequent dosages of premedications with dexamethasone, diphenhydramine, and H2 blockers may be reduced at the investigator's discretion.

Patients must be attended by medical personnel for the first 15 minutes of infusion and then have blood pressure checked every 15 minutes for 1 hour, then as needed. Medications for acute management of anaphylaxis should be readily available in the location where the patient is being treated.

7.2.3 Carboplatin
The dose of carboplatin is area under the curve (AUC) = 2 over 1 hour on days 1, 8, 15, 22, 29, and 36. The dose of carboplatin is calculated as follows, using the Calvert formula based on creatinine clearance: Total dose (mg) = Target AUC (in mg/mL per min) x (Estimated GFR + 25).

The GFR should not exceed 125 ml/min. If the calculated GFR based on the Calvert formula is greater than 125 ml/min, a GFR of 125 ml/min should be used. The maximum carboplatin dose for an AUC = 2 should not exceed 300 mg.

Carboplatin will be administered after paclitaxel. Patients will receive appropriate antiemetics and supplemental hydration as per their institutional protocol.

7.3 Study Agents
7.3.1 Trastuzumab (Herceptin®) [NSC 688097; IND 6667]

7.3.1.1 Investigator Brochure
All investigators who receive a copy of the protocol also should obtain a copy of the Investigator's Brochure (IB). Investigator's Brochures are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by e-mailing the IB Coordinator (ibcoordinator@mail.nih.gov) or by calling the IB Coordinator at 301-496-5725.

7.3.1.2 Formulation
Trastuzumab is supplied as a lyophilized powder in multidose vials, containing 440 mg of trastuzumab, and one 20 mL vial of Bacteriostatic Water for Injection (BWFI), USP (containing 1.1% benzyl alcohol), for reconstitution. The drug is formulated in histidine, trehalose, and polysorbate 20. Each vial is reconstituted with only 20 mL of BWFI. The reconstituted solution contains 21 mg/mL trastuzumab and will be added to an infusion bag containing 250 mL of 0.9% Sodium Chloride for Injection, USP (Dextrose solutions should not be used) and the bag gently inverted to mix the solution. For patients with a known hypersensitivity to benzyl alcohol (the preservative in Bacteriostatic Water for Injection) reconstitute trastuzumab with Sterile Water for Injection (SWFI), USP. Trastuzumab reconstituted with SWFI must be used immediately. Discard the SWFI-reconstituted trastuzumab vial following a single use. Do not mix or dilute trastuzumab with other drugs.

7.3.1.3 Administration
The initial dose of trastuzumab will be administered over a 90-minute period. If this dose is 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 fever or chills), subsequent infusions may be shortened only after a dose is well tolerated. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

7.3.1.4 Storage and Stability
Trastuzumab must be stored in a refrigerator (2°C-8°C) immediately upon receipt to ensure optimal retention of physical and biochemical integrity. DO NOT FREEZE. The reconstituted formulation (440-mg vial) is designed for multiple uses. Unused drug may be stored for 28 days at 2°C-8°C (36°F-46°F). Discard any remaining reconstituted solution after 28 days. Reconstituted Trastuzumab should be a colorless to pale yellow, transparent solution.

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

Genentech will supply trastuzumab free of charge to patients on study, and it will be distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation
Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

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 [study agent] 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 149, Bethesda, MD 20892.] All forms can be accessed on the NCI web site, [http://ctep.cancer.gov/forms/index.html](http://ctep.cancer.gov/forms/index.html).
Adverse Events
Comprehensive Adverse Events and Potential Risks list (CAEPR)
for Trastuzumab (NSC 688097)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the 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.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers](http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers) for further clarification. *Frequency is provided based on 2708 patients*. Below is the CAEPR for trastuzumab.

### Adverse Events with Possible Relationship to Trastuzumab (Herceptin) 
(CTCAE 4.0 Term)  

<n= 2708>

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Febrile neutropenia&lt;sup&gt;2&lt;/sup&gt;</td>
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</tr>
<tr>
<td><strong>CARDIAC DISORDERS</strong></td>
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<td></td>
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<tr>
<td>Cardiac arrest</td>
<td></td>
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<td>Cardiac disorders - Other (cardiomyopathy)</td>
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</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
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<td></td>
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<tr>
<td>Pericarditis</td>
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<td></td>
<td></td>
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<tr>
<td>Sinus tachycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
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<td></td>
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<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
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<tr>
<td>Diarrhea</td>
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<td></td>
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<tr>
<td>Mucositis oral</td>
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<td></td>
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<tr>
<td>Nausea</td>
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<td></td>
<td></td>
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<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fatigue</td>
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<td>Flu like symptoms</td>
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<tr>
<td>Non-cardiac chest pain</td>
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<tr>
<td>Pain</td>
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</tr>
<tr>
<td>Infusion related reaction</td>
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<tr>
<td><strong>IMMUNE SYSTEM DISORDERS</strong></td>
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<tr>
<td>Allergic reaction&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Anaphylaxis</td>
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<tr>
<td><strong>INFECTIONS AND INFESTATIONS</strong></td>
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<td></td>
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<tr>
<td>Infection&lt;sup&gt;4&lt;/sup&gt;</td>
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</tr>
<tr>
<td><strong>INVESTIGATIONS</strong></td>
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</tbody>
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Version 2.1, March 23, 2010<sup>1</sup>
<table>
<thead>
<tr>
<th>METABOLISM AND NUTRITION DISORDERS</th>
<th>Alkaline phosphatase increased</th>
<th>Aspartate aminotransferase increased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac troponin I increased</td>
<td>GGT increased</td>
</tr>
<tr>
<td></td>
<td>GGT increased</td>
<td>Neutrophil count decreased(^2)</td>
</tr>
<tr>
<td></td>
<td>White blood cell decreased</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</th>
<th>Aspartate aminotransferase increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>Neutrophil count decreased(^2)</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
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<table>
<thead>
<tr>
<th>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)</th>
<th>Anorexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor pain</td>
<td></td>
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<table>
<thead>
<tr>
<th>NERVOUS SYSTEM DISORDERS</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral sensory neuropathy</td>
<td></td>
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<table>
<thead>
<tr>
<th>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</th>
<th>Hypoxia(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult respiratory distress syndrome(^3)</td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm(^3)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
</tr>
<tr>
<td>Dyspnea(^2)</td>
<td></td>
</tr>
<tr>
<td>Hypoxia(^3)</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion(^2)</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis(^5)</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td></td>
<td>Pulmonary fibrosis</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</th>
<th>Rash maculo-papular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash acneiform</td>
<td></td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VASCULAR DISORDERS</th>
<th>Hypertension(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypotension(^6)</td>
</tr>
</tbody>
</table>

|                |                     |
|                |                     |
This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Fatal event when given in combination with Xeloda® (capecitabine) and Taxotere® (docetaxel).

Severe hypersensitivity reactions including, angioedema and pulmonary adverse events (e.g., hypoxia, dyspnea, pulmonary infiltrates, pleural effusion, and acute respiratory distress syndrome) have been reported.

Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Urticaria may be observed in conjunction with anaphylaxis.

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

**CARDIAC DISORDERS** - Myocardial infarction; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia

**EAR AND LABYRINTH DISORDERS** - Hearing impaired

**ENDOCRINE DISORDERS** - Hypothyroidism

**EYE DISORDERS** - Blurred vision; Extraocular muscle paresis

**GASTROINTESTINAL DISORDERS** - Colitis; Dyspepsia; Enterocolitis; Esophageal ulcer; Gastritis; Pancreatitis; Upper gastrointestinal hemorrhage

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Sudden death NOS

**IMMUNE SYSTEM DISORDERS** - Immune system disorders - Other (autoimmune thyroiditis)

**INVESTIGATIONS** - Alanine aminotransferase increased; Blood bilirubin increased; Creatinine increased; Platelet count decreased

**METABOLISM AND NUTRITION DISORDERS** - Hypomagnesemia; Hyponatremia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Avascular necrosis; Generalized muscle weakness; Muscle weakness left-sided; Muscle weakness lower limb; Muscle weakness right-sided; Muscle weakness trunk; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (myopathy)

**NERVOUS SYSTEM DISORDERS** - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dizziness; Hydrocephalus; Ischemia cerebrovascular; Neuralgia; Seizure; Syncope

**PSYCHIATRIC DISORDERS** - Anxiety; Confusion; Depression; Psychosis

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Fallopian tube obstruction; Prostatic obstruction; Spermatic cord obstruction; Uterine obstruction; Vaginal obstruction

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Apnea; Laryngeal edema; Pharyngolaryngeal pain; Pneumothorax; Pulmonary hypertension; Voice alteration

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Nail loss; Pruritus; Skin ulceration

**VASCULAR DISORDERS** - Thromboembolic event

**Note:** 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.

7.3.2 Paclitaxel

Refer to the package insert for additional information.

7.3.2.1 *Formulation*

Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf-life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours at ambient temperature (27°C).
7.3.2.2 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 will be diluted to a final concentration of 0.3 to 1.2 mg/ml in D$_3$W, USP, in glass or polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVPs) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the intravenous 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.

7.3.2.3 Administration
Paclitaxel, at the appropriate dose and dilution, will be given as a 1-hour infusion. The paclitaxel is mixed in D$_3$W or NS with 0.22 m in-line filter. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the intravenous administration sets (polyethylene or polyolefin) that are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

Caution is warranted when paclitaxel is concomitantly administered with known substrate or inhibitors of CYP2C8 and CYP3A4.

7.3.2.4 Storage
Paclitaxel vials should be stored between 20°-25°C (68°-77°F).

7.3.2.5 Adverse Effects
- Hematologic: Myelosuppression
- Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain
- Heart: Arrhythmias, heart block, hypertension
- Neurological: Sensory and peripheral neuropathy
- Allergy: Severe anaphylactic reactions
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), hypotension, irritation to the injection site, mucositis

7.3.2.6 Supply
Commercially available.

7.3.3 Carboplatin
Refer to the package insert for additional information.

7.3.3.1 Formulation
Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol.

7.3.3.2 Administration
Carboplatin will be infused intravenously over 1 hour. The dose of carboplatin is area under the curve (AUC) = 2. The dose of carboplatin is calculated as follows, using the Calvert formula based on creatinine clearance: Total dose (mg) = Target AUC (in mg/mL per min) x (Estimated GFR + 25)

The GFR should not exceed 125 ml/min. If the calculated GFR based on the Calvert formula is greater than 125 ml/min, a GFR of 125 ml/min should be used. The maximum carboplatin dose for an AUC = 2 should not exceed 300 mg.

In the absence of new renal obstruction or other renal toxicity greater than or equal to CTCAE (per Section 7.8) grade 2 (serum creatinine >1.5 x ULN), the dose of carboplatin will not be recalculated for subsequent cycles, but will be subject to dose modification as noted. In patients with an abnormally low serum creatinine (≤ 0.6 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using a
minimum value of 0.6 mg/dl. If a more appropriate baseline creatinine value is available within 4 weeks of treatment that may also be used for the initial estimation of GFR.

**Note:** The carboplatin dose is calculated in mg, not mg/m². For the purposes of this protocol, the GFR is considered equivalent to the creatinine clearance. Creatinine clearance (CrCL) can either be measured or estimated using the formula:

\[
\text{CrCL} = \frac{(140-\text{age}) \times \text{wt (kg)} \times (0.85 \text{ if female})}{72 \times \text{creatinine (mg/dl)}}
\]

### 7.3.3.3 Adverse Events
- **Hematologic:** Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leucopenia, and anemia are common but typically resolve by day 28 when carboplatin is given as a single agent.
- **Allergic reactions:** Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy. Desensitization per the allergy team is allowed.
- **Neurologic:** Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.
- **Gastrointestinal:** Nausea and vomiting are the most common gastrointestinal events; both usually resolve within 24 hours and respond to antiemetics. Other gastrointestinal events include diarrhea, weight loss, constipation, and gastrointestinal pain.
- **Hepatic toxicity:** Elevated alkaline phosphatase, total bilirubin, and SGOT have been reported.
- **Other:** Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

### 7.3.3.4 Preparation
When available, prediluted vials of carboplatin should be utilized. Otherwise, the preparation of carboplatin should proceed as described below:

Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL:

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Diluent volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>5mL</td>
</tr>
<tr>
<td>150 mg</td>
<td>15 mL</td>
</tr>
<tr>
<td>450 mg</td>
<td>45 mL</td>
</tr>
</tbody>
</table>

Carboplatin reacts with aluminum to form a precipitate and cause a loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

### 7.3.5 Storage and Stability
Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30°C or 59-86°F) and protected from light. When prepared as described above, carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

### 7.3.6 Supply
Commercially available.
7.4 **Clinical Trials Agreement**

The agent supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company (hereinafter referred to as a 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 ([http://ctep.cancer.gov/industry/ipo.html](http://ctep.cancer.gov/industry/ipo.html)) contained within the terms of award, apply to the use of the Agent in this study:

1. The Agent may not be used for any purpose outside the scope of this protocol, nor can the Agents be transferred or licensed to any party not participating in the clinical study. The Collaborator’s data for the Agent are confidential and proprietary to the 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](http://ctep.cancer.gov).

2. For a clinical protocol where there is an investigational Agent used in combination with another investigational Agents, each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as “Multi-Party Data”):
   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the 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.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to the Collaborator for advisory review and comment prior to submission for publication. The Collaborator will have 30 days from the date of receipt for review. The 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 the Collaborator’s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to the 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:
The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

7.5 **Dose Modifications: Trastuzumab**

**NOTE:** The trastuzumab dose will not be modified.

7.5.1 **Infusion-Associated Symptoms**

Treatment with trastuzumab will be permanently discontinued in any patient who experiences either an anaphylactic reaction (a Grade 4 [CTCAE version 4.0] allergic/hypersensitivity reaction) or a grade 3 reaction that is consistent with an allergic reaction characterized by severe bronchospasm.

7.5.2 **Cardiac Toxicity: Asymptomatic Decrease in LVEF**

The decision to continue or stop trastuzumab is based on the measured LVEF as it relates to the facility's lower limit of normal (LLN) and change in the LVEF from baseline.

<table>
<thead>
<tr>
<th>Relationship of LVEF to facility's LLN</th>
<th>Decrease of &lt;10% from baseline</th>
<th>Decrease of 10-15% from baseline</th>
<th>Decrease of ≥16% from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within normal limits</td>
<td>Continue</td>
<td>Continue</td>
<td>Hold trastuzumab and repeat MUGA/Echo in 4 weeks</td>
</tr>
<tr>
<td>1-5% below LLN</td>
<td>Continue trastuzumab and repeat MUGA/Echo in 4 weeks</td>
<td>Hold trastuzumab and repeat MUGA/Echo in 4 weeks</td>
<td>Hold trastuzumab and repeat MUGA/Echo in 4 weeks</td>
</tr>
<tr>
<td>≥ 6% below LLN</td>
<td>Continue trastuzumab and repeat MUGA/Echo in 4 weeks</td>
<td>Hold trastuzumab and repeat MUGA/Echo in 4 weeks</td>
<td>Hold trastuzumab and repeat MUGA/Echo in 4 weeks</td>
</tr>
</tbody>
</table>

- In light of the variability inherent in the assessment of ejection fraction, consideration should be given to repeating the study to confirm an observed decline.
- Trastuzumab must be permanently discontinued if 2 consecutive "hold" categories occur.
- If the LVEF is maintained at a "Continue trastuzumab and repeat MUGA/Echo in 4 weeks" or improves from a "Hold" to a "Continue", additional MUGA scans or echocardiograms prior to the next required MUGA scan/echocardiogram may be obtained at the discretion of the investigator.

Patients with an asymptomatic > 20% decrease in LVEF or a decrease of LVEF > 10% below the institutional lower limit of normal should be considered for treatment of incipient congestive heart failure (CHF). Trastuzumab will be discontinued permanently in patients deemed to require treatment for cardiac dysfunction.

**Symptomatic decrease in LVEF:** Patients who develop signs or symptoms of CHF should receive treatment for CHF according to institutional guidelines (e.g., ACE inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics and cardiac glycosides). Trastuzumab will be discontinued permanently in patients deemed to require treatment for cardiac dysfunction. If cardiac toxicity occurs during chemoradiation then continuation of paclitaxel/carboplatin/radiation treatment is at the discretion of the investigator.

7.6 **Dose Modifications: Paclitaxel and Carboplatin**

All dose modifications will reflect the most severe toxicity that is observed, including hematologic and nonhematologic toxicity, skin toxicity, and creatinine toxicity.
7.6.1 Hematologic Adverse Events
The dose of paclitaxel, carboplatin, trastuzumab, and radiation will be modified according to blood counts on the day of treatment as shown in the table below. Dose reductions of paclitaxel and carboplatin are permanent.

<table>
<thead>
<tr>
<th>Treatment Day Blood Counts</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANC</strong> AND <strong>Platelet Count</strong></td>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td>&gt; 1,000 mcL AND &gt; 75,000 mcL</td>
<td>Full dosage paclitaxel, carboplatin, and trastuzumab.</td>
</tr>
<tr>
<td>500-999 mcL OR 50,000-75,000 mcL</td>
<td>Full dose trastuzumab. Hold carboplatin and paclitaxel. Recheck CBC weekly. When ANC &gt; 1,000 and Plt &gt; 75,000, resume paclitaxel at 1 dose level reduction and carboplatin at 1 dose level reduction.</td>
</tr>
<tr>
<td>&lt; 500 mcL OR &lt; 50,000 mcL</td>
<td>Hold XRT, carboplatin, paclitaxel, and trastuzumab; Recheck CBC weekly. When ANC &gt; 500 and Plt &gt; 50,000 resume XRT, full-dose trastuzumab. When ANC &gt; 1,000 and Plt &gt; 75,000 resume paclitaxel and carboplatin and reduce both by 1 dose level.</td>
</tr>
</tbody>
</table>

Patients who experience 4 episodes of ANC < 500 mcL or platelets < 50,000 mcL may complete radiation and trastuzumab on study but will not receive additional carboplatin and paclitaxel.

Dose levels for paclitaxel are as follows:

- **Weekly Paclitaxel Dose**: 50 mg/m²
- **Dose Level -1**: 40 mg/m²
- **Dose Level -2**: 30 mg/m²
- **Dose Level -3**: 20 mg/m²

There will be no dose level reductions below a weekly dose of 20 mg/m².

Dose levels for carboplatin are as follows:

- **Weekly Carboplatin Dose**: AUC = 2
- **Dose Level -1**: AUC = 1.5
- **Dose Level -2**: AUC = 1.0
- **Dose Level -3**: AUC = 0.5

There will be no dose level reductions below a weekly dose AUC = 0.5.

7.6.2 Nonhematologic Adverse Events
Nonhematologic adverse events that will require dose reductions of paclitaxel or carboplatin include diarrhea, mucositis, esophagitis, and nausea/vomiting/dehydration despite adequate treatment with antiemetic therapy (including substance p antagonists and 5-HT3 antagonists). Dose reductions of paclitaxel and carboplatin are permanent.
### Toxicity Grade Agent Modification

<table>
<thead>
<tr>
<th>Episode</th>
<th>Grade</th>
<th>Agent</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>≥ grade 3</td>
<td>Carboplatin, Paclitaxel, Trastuzumab</td>
<td>Hold until ≤ grade 2; resume, dose, reducing carboplatin by 1 dose level and paclitaxel by 1 dose level; no dose reduction for trastuzumab</td>
</tr>
<tr>
<td>2nd</td>
<td>≥ grade 3</td>
<td>Carboplatin, Paclitaxel, Trastuzumab</td>
<td>Hold until ≤ grade 2; resume dose, reducing carboplatin by 1 dose level and paclitaxel by 1 dose level; no dose reduction for trastuzumab</td>
</tr>
<tr>
<td>3rd</td>
<td>≥ grade 3</td>
<td>Carboplatin, Paclitaxel, Trastuzumab</td>
<td>Discontinue all carboplatin, paclitaxel. Resume trastuzumab when ≤ grade 2</td>
</tr>
<tr>
<td>Paclitaxel infusion-related reaction</td>
<td>≥ grade 4</td>
<td>Paclitaxel</td>
<td>Discontinue paclitaxel. Trastuzumab, carboplatin, and radiation may be continued.</td>
</tr>
<tr>
<td>Carboplatin infusion-related reaction</td>
<td>≥ grade 4</td>
<td>Carboplatin</td>
<td>Discontinue carboplatin. Trastuzumab, paclitaxel, and radiation may be continued.</td>
</tr>
</tbody>
</table>

#### 7.7 Modality Review

The Medical Oncology Co-Chairs, Dr. Howard Safran and Dr. Lawrence Leichman, MD will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy 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/Acceptable Variation, Not Per Protocol, and Not Evaluable.** A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Safran and Leichman will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Safran and Dr. Leichman will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. This will continue as complete data is available for subsequent cases. 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.

#### 7.8 Adverse Events

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site ([http://ctep.cancer.gov](http://ctep.cancer.gov)).

All adverse events (AEs) as defined in the tables in Section 7.9 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/gadeers_main$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site ([http://www.rtog.org/members/toxicity/main.html](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. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497 only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into AdEERS by the original submitter at the site.

Adverse Events (AEs)

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 (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: 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 7.9 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.

Serious Adverse Events (SAEs)

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.

Pharmacologically 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 via the AdEERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCARE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

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

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

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days\(^1\) of the Last Dose of the Investigational Agent [trastuzumab] and the Commercially Available Agents in this Study

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5(^2)</th>
<th>Grades 4 &amp; 5(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unrelated</strong></td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td><strong>Unlikely</strong></td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>24-Hour; 5 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td><strong>Definite</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 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

\(^2\) 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.

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 assigned during trial registration on all reports.

8.0 SURGERY

8.1 If a stent is placed for nutritional support, it must be placed after imaging and EUS.

8.2 All patients are required to undergo endoscopy with biopsy of the tumor site 4 to 6 weeks after the last radiation treatment. If there is no evidence of metastatic disease, on CT chest/abdomen/pelvis or PET/CT performed on completion of radiotherapy, curative resection will be performed 5 to 8 weeks after completion of induction therapy. If studies indicate metastatic disease, patients will receive no further protocol treatment.

8.3 Surgical resection may include transthoracic (Ivor Lewis), transhiatal, McKeon, minimally invasive or thoracoabdominal esophagectomy. Overlying mediastinal pleura and adjacent soft tissues 5 cm proximal and distal to the primary lesion should be included to insure an adequate radial margin. It is recommended that nodal staging include levels 7, 8, 9, 15, 16, 17 and 20.

8.4 The resection will be classified as R0 (all gross tumor removed, microscopically negative margins); R1 (all gross tumor removed, microscopically positive margins); or R2 (gross residual tumor).

8.5 As surgery is a component of both study arms, a full surgical Quality Assurance Review is required for this study; this will be performed by the Surgical Oncology Co-Chair, Carolyn Reed, who will perform the review after complete data for 20 cases have been received at RTOG Headquarters. Dr. Reed 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 have been received at RTOG Headquarters, whichever occurs first. Surgical review requires complete operative and pathology reports.

9.0 OTHER THERAPY

9.1 Permitted Therapy
  Patients may receive all concomitant therapy deemed necessary to provide adequate support, with the exception of the therapies detailed in Section 9.2. In addition, myeloid growth factors are permitted only to treat grade 4 neutropenia. Erythropoietins are allowed to treat anemia according to institutional guidelines.

9.2 Non-Permitted Therapy
  9.2.1 Other investigational agents;
  9.2.2 Other cytotoxic agents;
  9.2.3 Other radiotherapy.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission. If the patient consents to participate in the optional tissue/specimen banking in this study, the site is required to submit the patient’s specimens as specified in Section 10.0 of the protocol. Note: Sites are not permitted to delete the tissue component from the protocol or from the sample consent.
10.1 Tissue/Specimen Submission

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 encourages participants in protocol studies to consent to the banking of their tissue, blood, and urine. The RTOG Biospecimen Resource provides 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.

In this study, tissue must be submitted for the purpose of determining if HER2 is overexpressed (mandatory for eligibility) and for specimen banking (recommended).

10.2 Tissue Collection for Central Review of HER2 for Eligibility – Mandatory (Step 1 Registration)

10.2.1 It is highly recommended that tissue be sent as early as possible during a patient’s clinical evaluation for HER2 determination. Determination of Step 2 patient eligibility does not need to be completed prior to sending tumor tissue for HER2 determination. The following are recommendations to achieve rapid and efficient HER2 testing:

- If there is adequate tissue remaining after the initial endoscopic biopsy, this tissue should be sent to Dr. Resnick at Rhode Island Hospital, preferably in the form of a paraffin block or alternatively 12 unstained slides.
- A second biopsy to obtain additional pathologic material is highly recommended from the endoscopic ultrasound. If the pathologic diagnosis of esophageal cancer has already been made from the initial endoscopy, it is highly recommended that tissue (in the form of a paraffin block) obtained at the endoscopic ultrasound be directly sent to Dr. Resnick without additional pathologic evaluation at the referring institution.
- If tissue from the initial endoscopy is available and the endoscopic ultrasound has not yet been performed, it is recommended that biopsy material from the initial endoscopy be sent to Dr. Resnick at Rhode Island Hospital as soon as it is available. Material from the EUS should be sent separately as soon as the EUS has been completed (for HER2 positive patients only see Section 10.3.3).

10.2.2 Required Pathologic Material for HER2 Testing

- Representative H & E stained slides
- Corresponding paraffin-embedded tissue block of the tumor; if the institution is not able to release the blocks, then 12 unstained 5-micron sections on plus slides from the primary block.
- 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. Histologic evaluation of submitted tissue by the referring institutions pathology department is not required.
- A Specimen Form (SP) stating that the tissue is being submitted for HER2 testing must accompany the specimen. Sites can access the form (no password required) at http://www.rtog.org/members/forms/list.html (under “RTOG 1010”). The form must be filled out completely and indicate whether the patient has consented to banking of any left over tissue. This transmittal form (SP) is protocol specific and is used for HER2 testing exclusively. (The generic ST form is not to be used.)
- Included with the submitted pathologic material should be the name, e-mail address, and FAX number of the responsible referring physician and the site principal investigator. The physicians will be contacted (generally by e-mail) by Drs. Safran or Resnick or an appointed assistant with the results of HER2 testing.
10.2.3  Mailing Information
Pathologic material should be sent by FEDEX to

Murray Resnick, MD, PhD
Director of Surgical Pathology
Department of Pathology
The Rhode Island Hospital
593 Eddy Street, Providence RI 02930
401-444-4380
mresnick@lifespan.org

10.2.4  Determination of HER2
To determine HER2 status, dual IHC and FISH testing will be performed and the IHC scoring system will per done as per the modified IHC scoring validated in the phase III ToGA study and as reviewed by Hofmann et al (2008). This HER2 scoring takes into account that the HER2 Testing scoring methodology for gastric cancer differs from that used for breast cancer and that the use of the breast testing methodology can potentially under-represent the percentage of patients who might test positive and thus be eligible for treatment on the study. Gastric tumor cells lining the lumen may not stain on the luminal portion of the cell and thus may not have complete membrane staining. In the modified gastric system (Hofmann 2008) this pattern will be considered positive but would be misinterpreted as negative if the breast cancer scoring system were utilized. Therefore, HER2 positivity will be defined using the modified gastric system, where IHC 3+ will be defined as moderate to strong complete or basolateral membrane staining in > 10% of tumor cells, and IHC2+ if the staining is weak to moderate. As we will be dealing with biopsy specimens cohesive clusters or clones will be considered positive irrespective of size (<10%). FISH will be defined as positive if the HER2 to CEP17 ratio is > 2.0. For tumors with IHC of 0, +1 or +2 by IHC, if they are FISH+ they will be considered to be HER2 positive.

10.2.4.1  Immunohistochemistry (IHC) and Fluorescence In Situ Hybridization (FISH)
IHC analysis of samples will be performed using the HercepTest kit (Dako) and FISH will be performed with the PathVysion™ detection system (an FDA approved in vitro diagnostic test) containing a locus-specific HER-2neu probe (17q11.2-q12-LSI HER-2/neu Spectrum Orange) and chromosome 17-centromere probe (17q11.1-q11.1-CEP17 Spectrum Green). Digestion and pretreatment of the tissue are performed according to the vendor protocols, along with appropriate positive and negative controls. A total of 120 nuclei are analyzed to determine the amplification status of HER-2/neu gene on chromosome 17. Two independent observers score the results and the results are verified by a pathologist. A ratio between chromosome 17 signals and HER-2/neu gene is calculated to determine the copy number of the Her-2/neu gene.

Quality Control: The testing is carried out following ASCO and CAP guidelines. The length of time that the tissue is fixed is recorded for each specimen. Each FISH run is carried out with both a positive and negative control. Each run is scored by 2 independent observers and checked by a pathologist before the results are released. If there is a discrepancy greater than 0.2 between the 2 scores additional cells are scored and a third independent scorer will be used as needed. All results in the equivocal range (Her2neu/CEPH ratio of 1.8-2.1) are repeated and/or sent out depending on the case.

Close collaboration with the referring physicians and the molecular biology laboratory by e-mail (with Drs. Murray Resnick and Howard Safran) will be ongoing throughout the study to ensure that FISH results will be available.

10.2.4.2  Process for Evaluating HER2 Status
Dr. Resnick's laboratory will report HER2 results by IHC within 3 business days and HER2 by FISH within 7 business days from receipt of all required pathology materials. HER2 results will be emailed to the two site contacts listed on the pathology submission form (i.e. participating site PI and site contact) and the RTOG registration office.

The institutional pathologist will be notified in the event that the block may be depleted. The paraffin-embedded blocks will be available to the submitting institution upon specific request.
to accommodate individual patient management. Sites requesting that tissue blocks be returned for local testing purposes must confirm with appropriate personnel (e.g., local pathologist, laboratories) that no tissue blocks were retained at the local site. Please use retained materials before requesting the RTOG to return submitted tissue blocks to the site.

10.3 Specimen Collection for Banking - Recommended

For patients who have consented to participate in the optional specimen banking component of the study (See Appendix I).

An important objective of this study is to create a tissue bank for patients with esophageal adenocarcinoma. Specific translational projects will be determined after accrual is completed and closer to the time that the efficacy data will be available, based on the state of the science at that time. Potential projects could include mRNA of ERCC1, TS, miRNA analysis or gene expression analysis via laser capture microdissection, SNP analysis, topoisomerase II or downstream phosphorylated proteins involved in the HER2 pathway. Studies from the blood collection could include SNP analysis (DNA repair, HER2, VEGF, and EGFR pathways.) Blood markers that could correlate to cardiac damage from trastuzumab could be analyzed.

- All patients will be given the opportunity to participate in tissue banking. If the patient consents, then any tumor tissue remaining after HER2 determination will be sent from Dr. Resnick's laboratory to the RTOG Biospecimen Resource.
- For HER2 positive patients, a representative H&E stained slide and corresponding paraffin-embedded tissue block of the tumor removed at esophagectomy surgery should be submitted to the RTOG Biospecimen Resource for banking; if the institution is not able to release the blocks, then a 2 mm punch of the FFPE block is acceptable. A punch kit and instructions can be requested at rtog@ucsf.edu
- For HER2 positive patients, plasma and urine will be collected from all consenting patients at baseline and prior to surgery and whole blood will be collected once at baseline (or at any other time point) and will be shipped directly to the RTOG Biospecimen Resource (see Section 10.3.3).

See Appendix VI for detailed collection instructions, including information pertaining to collection kits. Note: Kits include a shipping label.

10.3.1 The following must be provided to the RTOG Biospecimen Resource:
(1) 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; (2) a Specimen Transmittal Form documenting the date of collection of the whole blood, plasma, and urine; (3) the RTOG protocol number; (4) the patient’s case number; (5) sample collection time point (0 time, # days post-chemoradiation); and (6) method of storage, for example, stored at -80° C.

10.3.2 Frozen Biospecimen Storage Conditions

Store frozen biospecimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.
## 10.3.3 Specimen Collection Summary

<table>
<thead>
<tr>
<th>Specimen Collection Summary</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mandatory Specimens (All Patients)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specimens:</td>
<td>Collected When:</td>
<td>Submitted As:</td>
<td>Shipped:</td>
</tr>
<tr>
<td>1 block primary tumor OR 12 unstained slides from the primary block</td>
<td>Removed at diagnostic endoscopy</td>
<td>Formalin fixed paraffin-embedded block</td>
<td>Dr. Resnick Rhode Island Hospital, Providence</td>
</tr>
<tr>
<td><strong>Mandatory Specimens (HER2-Positive Patients Only)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specimens:</td>
<td>Collected When:</td>
<td>Submitted As:</td>
<td>Shipped:</td>
</tr>
<tr>
<td>1 block primary tumor OR 12 unstained slides from the primary block</td>
<td>Removed at endoscopic ultrasound</td>
<td>Formalin fixed paraffin-embedded block</td>
<td>Dr. Resnick Rhode Island Hospital, Providence</td>
</tr>
<tr>
<td><strong>Recommended Specimens (HER2-Positive Patients Only)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specimens:</td>
<td>Collected When:</td>
<td>Submitted As:</td>
<td>Shipped:</td>
</tr>
<tr>
<td>1 block residual primary tumor or 2-mm punch of block</td>
<td>Removed at esophagectomy surgery</td>
<td>Formalin fixed paraffin embedded</td>
<td>RTOG Biospecimen Resource, San Francisco Shipped ambient</td>
</tr>
<tr>
<td>5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for plasma</td>
<td>Before treatment start and after chemoradiation prior to surgery</td>
<td>Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (up to 10)</td>
<td>RTOG Biospecimen Resource, San Francisco Plasma sent frozen on dry ice via overnight carrier (Monday-Wednesday; Canada: Monday-Tuesday) See Appendix VI</td>
</tr>
<tr>
<td>5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and aliquotted for DNA</td>
<td>Before treatment start (or at any visit during or after treatment)</td>
<td>Frozen whole blood samples containing 1 mL per aliquot in 1 mL cryovials. (up to 5)</td>
<td>RTOG Biospecimen Resource, San Francisco Whole blood sent frozen on dry ice via overnight carrier (Monday-Wednesday; Canada: Monday-Tuesday) See Appendix VI</td>
</tr>
<tr>
<td>10-20 mL clean-catch urine</td>
<td>Before treatment start and after chemoradiation prior to surgery</td>
<td>Two 10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes.</td>
<td>RTOG Biospecimen Resource, San Francisco Urine sent frozen on dry ice via overnight courier (Monday-Wednesday; Canada: Monday-Tuesday) See Appendix VI</td>
</tr>
</tbody>
</table>
10.3.4 Submit materials for Tissue Banking as follows:

Courier Address (Fed Ex, 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

10.4 Reimbursement
RTOG will reimburse institutions for submission of protocol-specified biospecimen materials sent to the RTOG Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement & Case Credit Schedule found on the RTOG Web site (http://www.rtog.org/pdf_document/RTOG_STUDY_LIST.pdf). Biospecimen payments will be processed quarterly and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.5 Confidentiality/Storage
(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.5.1 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.

10.5.2 Specimens for central review will be retained until the study is terminated. 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 ASSESSMENTS
11.1 Study Parameters: See Appendix II.

11.2 Measurement of Response
- Pathologic response will be evaluated after the patient has had surgery and will be based on the pathology review of the submitted surgical specimen according to the following:
  - Pathologic Complete Response (pCR): On review of the resected esophageal specimen and accompanying lymph nodes no cancer is recognized by the pathologist and margins are free of tumor.
  - Microscopic Cancer: Gross tumor is not seen by the pathologist but tumor remains in the microscopic analysis or any part of the entire specimen submitted for pathology review.
  - No Response: Gross cancer is found on pathologic examination of the resected esophageal cancer and draining lymph nodes.

11.3 Criteria for Discontinuation of Protocol Treatment
- Progression of disease
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), as defined in Section 6.0 and/or 7.0
- Patient decides to withdraw from the study

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.
11.4 Quality of Life and Health Utility Assessments

11.4.1 *The Functional Assessment of Cancer Therapy for Esophageal Cancer (FACT-E)* is a multidimensional, QOL instrument specifically designed and validated for use with patients with esophageal cancer patients that the patient can complete in 10 minutes. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. Note: The FACT-E has been translated into 16 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at [http://www.facit.org/translation/licensure.aspx](http://www.facit.org/translation/licensure.aspx).

11.4.2 *The EuroQol (EQ-5D)* is a two-part questionnaire that the patient can complete in approximately 5 minutes. Note: The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at [http://www.euroqol.org/](http://www.euroqol.org/). The site research nurse or CRA should encourage the patient not to skip questions on the EQ-5D or take breaks during the completion of this questionnaire, as this will invalidate the assessment. If this occurs, sites will document it on the Health Utility Measurement (HP) form.
### 12.0 DATA COLLECTION

Data should be submitted to:

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

*If a data form is available for web entry, it must be submitted electronically.

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

#### 12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen Form (SP)</td>
<td>To be submitted with tumor sample for HER2 testing to Dr. Resnick (see Section 10.2.2) after Step 1 registration</td>
</tr>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 wks of Step 2 registration</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Quality of Life/Health Utility Forms</td>
<td></td>
</tr>
<tr>
<td>▪ FACT-E (FA)</td>
<td></td>
</tr>
<tr>
<td>▪ EQ-5D (HP)</td>
<td></td>
</tr>
<tr>
<td>Treatment Form (TF)</td>
<td>Within 1 wk of concurrent systemic treatment completion</td>
</tr>
<tr>
<td>Radiotherapy Form (T1) [copy to HQ and ITC]</td>
<td>Within 1 wk of RT end</td>
</tr>
<tr>
<td>Daily Treatment Record (T5) [copy to HQ and ITC]</td>
<td></td>
</tr>
<tr>
<td>Initial Follow-Up Form (FS)</td>
<td>Just prior to resection (must include all toxicities up to the surgical resection)</td>
</tr>
<tr>
<td>Surgical Form (S1)</td>
<td>Within 4 wks post surgical resection</td>
</tr>
<tr>
<td>Operative Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Maintenance Treatment Form (SF)</td>
<td>Within 1 wk of completion of cycles 1-5, 6-10 and 11-13</td>
</tr>
<tr>
<td>Quality of Life/Health Utility Forms</td>
<td></td>
</tr>
<tr>
<td>▪ FACT-E (FA)</td>
<td>6 wks post chemo/RT but prior to esophagectomy, 1 yr from start of treatment, and 2 yrs from start of treatment</td>
</tr>
<tr>
<td>▪ EQ-5D (HP)</td>
<td>1 yr from start of treatment and 2 yrs from start of treatment</td>
</tr>
<tr>
<td>Follow-Up Form (F1)</td>
<td>Every 4 mos from the end of RT x 2 yrs, then annually</td>
</tr>
</tbody>
</table>

PET/CT or CT Scan Report (C3)

---

*RTOG 1010*
### 12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preliminary Dosimetry Information (DD)</strong></td>
<td>Within 1 week of RT start</td>
</tr>
<tr>
<td>†Digital Data Submission Form (DDSI)</td>
<td></td>
</tr>
<tr>
<td>CT data, critical normal structures, all GTV, CTV, and PTV contours</td>
<td></td>
</tr>
<tr>
<td>Digital beam geometry for initial and boost beam sets</td>
<td></td>
</tr>
<tr>
<td>Doses for initial and boost sets of concurrent treated beams</td>
<td></td>
</tr>
<tr>
<td>Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)</td>
<td></td>
</tr>
<tr>
<td>Hard copy or JPEG isodose distributions for total dose plan as described in QA guidelines† (T6)</td>
<td></td>
</tr>
<tr>
<td><strong>Final Dosimetry Information</strong></td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1) [copy to HQ and ITC]</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5) [copy to HQ and ITC]</td>
<td></td>
</tr>
<tr>
<td>Modified digital patient data as required through consultation with Image Guided Therapy QA Center</td>
<td></td>
</tr>
</tbody>
</table>

†Available on the ATC web site, [http://atc.wustl.edu/](http://atc.wustl.edu/)

### 12.2.1 Digital Data Submission to ITC

Digital data submission may be accomplished using media or the Internet.

**For network submission:** The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to: itc@wustl.edu

**For media submission:** Please contact the ITC about acceptable media types and formats. Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

### 13.0 STATISTICAL CONSIDERATIONS

#### 13.1 Endpoints

##### 13.1.1 Primary Endpoint

Disease-free survival (failure: disease persistence or recurrence, or distant metastases, or second primary, or death due to any cause)

##### 13.1.2 Secondary Endpoints

- 13.1.2.1 Pathologic complete response at surgery
- 13.1.2.2 Overall survival (OS) (failure: death due to any cause)
- 13.1.2.3 Adverse events
- 13.1.2.4 Health-related quality of life (HRQoL) as measured by FACT-E
- 13.1.2.5 Quality adjusted survival
- 13.1.2.6 Molecular correlates of efficacy
- 13.1.2.7 Predictors of cardiotoxicity

#### 13.2 Stratification

Patients will be stratified before randomization with respect to the presence of adenopathy (No vs. Yes—celiac absent vs. Yes—celiac present ≤ 2 cm). The permuted block randomization
method described by Zelen (1974) will be used because it balances patient factors other than institution.

13.3 Sample Size and Power Justification

13.3.1 The sample size calculations are based on the primary hypothesis that the addition of trastuzumab during preoperative chemoradiation and for 12 months of maintenance following surgery will increase the median disease-free survival (DFS) from 15 months to 27 months, for HER2-overexpressing patients (HER2 positive) with esophageal adenocarcinoma.

The required sample size for the primary endpoint of DFS is based on the following conditions:

- DFS times are exponentially distributed with (at least approximately) constant hazards in both treatment arms
- The control arm will have a median DFS of 15 months (monthly hazard of 0.04621)
- The experimental arm will have a median DFS of 27 months (monthly hazard of 0.02567)
- Hazard ratio (experimental/control) = 0.56
- Two-sided test at $\alpha = 0.05$
- Statistical power of 90%
- 4 years of accrual with 2.5 years of follow-up
- Two interim significance tests and a final test are planned using the Haybittle-Peto (Lan 1983; O’Brien 1979) rule for efficacy and the Freidlin-Korn (Freidlin 2002) rule C for futility

Patients will be registered to the trial and then their HER2 status will be centrally evaluated. It is projected that 1 out of 3 patients evaluated will be HER2 positive. All patients who are HER2 positive will be randomized to the study treatment arms. Using the group sequential design method (Pocock 1977) with 3 interim analyses, 121 DFS events are required to detect an increase in median DFS from 15 months to 27 months, translating into a hazard ratio (experimental/control) of 0.56. Given the conditions above, a total sample size of 148 HER2 positive patients will be required to be accrued uniformly over 4 years with an additional 2.5 years of follow-up. Guarding against an ineligibility or lack-of-data rate of up to 7%, the targeted accrual of HER2 positive patients for this study will be 160 patients. It is projected that a total of 480 patients will need to be registered and evaluated for HER2 status.

13.3.2 Considerations for Increasing Sample Size

Two years after the study has been activated, if the following criteria are met:

- accrual is as projected
- toxicity is acceptable
- rate of patients screened positive for HER2 is as projected

then consideration will be given to increasing the sample size to detect a smaller increase in DFS, per the table below:

<table>
<thead>
<tr>
<th>Sample Sizes With 2-Sided Alpha = 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in Median DFS to (months)</td>
</tr>
<tr>
<td>27 – original</td>
</tr>
<tr>
<td>26.5</td>
</tr>
<tr>
<td>26</td>
</tr>
<tr>
<td>25.5</td>
</tr>
<tr>
<td>25</td>
</tr>
</tbody>
</table>

If there is a decision to increase the sample size, the extent of the increase will depend on the actual rates of accrual and HER2 positivity.

13.3.3 Patient Accrual

Patient accrual is projected to be 3 HER2 positive cases per month, with a ramp-up period in the first 6 months. The expected monthly accrual in months 1 through 3 and months 4 through
6 following activation are 0 and 1, respectively. If the total accrual during months 13 through 18 of the study is ≤ 20% of the targeted accrual (< 4 cases in total), then the protocol will be discontinued per NCI-CTEP accrual guidelines for phase III studies. If the total accrual during months 13 through 18 is between 21% and 49% (4 to 8 cases), then the protocol will continue to accrue subjects and will be evaluated again at the end of month 24. If the accrual during months 22 through 24 is at least 50% of the targeted accrual (≥ 5 cases in total), the NCI-CTEP accrual guidelines for phase III studies will have been met and the study will continue accrual; otherwise, the study will be discontinued.

13.4 Power Information for Health Reported Quality of Life – FACT-E

The Functional Assessment of Cancer Therapy – Esophagus (FACT-E) will be used to measure HRQOL, with the focus on the Esophageal Cancer Subscale (ECS). Protocol-eligible patients will be included in the QOL analysis only if they have provided baseline and at least one subsequent measurement. The FACT-E will be collected on all cases participating in this portion of the trial and will be collected at 4 time points: pretreatment (baseline); 6 to 8 weeks following chemoradiation with or without trastuzumab at the time of restaging prior to surgical resection; 1 year from start of treatment; and 2 years from start of treatment.

The primary HRQOL endpoint will be to determine whether the addition of trastuzumab to chemoradiation improves the FACT-E Esophageal Cancer Subscale (ECS) score, as measured by the proportion of patients on each treatment arm with improvement, defined as an increase in the ECS score of at least 5 points. Given the recent development and validation of this tool, the power calculations shown below cover a number of possible proportions for improvement over the control arm. The power calculations are all based on a 1-sided, \( \alpha = 0.05 \), chi-squared test and the assumption of an 80% participation rate.

### Power Calculations for ECS Score

<table>
<thead>
<tr>
<th>( p_0 )</th>
<th>( p_a )</th>
<th>( n/arm^* )</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.55</td>
<td>59</td>
<td>82</td>
</tr>
<tr>
<td>0.30</td>
<td>0.60</td>
<td>59</td>
<td>93</td>
</tr>
<tr>
<td>0.40</td>
<td>0.65</td>
<td>59</td>
<td>82</td>
</tr>
<tr>
<td>0.40</td>
<td>0.70</td>
<td>59</td>
<td>93</td>
</tr>
<tr>
<td>0.50</td>
<td>0.75</td>
<td>59</td>
<td>84</td>
</tr>
<tr>
<td>0.50</td>
<td>0.80</td>
<td>59</td>
<td>95</td>
</tr>
</tbody>
</table>

*If the participation rate is higher, there will be more power to detect the hypothesized differences; if the participation rate is lower, there will be less power.

13.5 Analysis Plan

All analyses will be done based on the assigned treatment arm for all eligible patients entered.

13.5.1 Statistical Methods

13.5.1.1 Disease-Free Survival

Disease-free survival (DFS) will be estimated by the Kaplan-Meier method (Kaplan 1958). The distribution of DFS estimates between the 2 arms will be compared using the log rank test (Mantel 1966). DFS time will be measured from the date of randomization to the date of first failure or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with DFS.

13.5.1.2 Overall Survival

Overall survival (OS) will be estimated by the Kaplan-Meier method (Kaplan 1958). The distribution of OS estimates between the 2 arms will be compared using the log rank test (Mantel 1966). OS time will be measured from the date of randomization to the date of first failure or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS.

13.5.2 Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:
- Patient accrual rate with a projected completion date (while the study is still accruing)
- Total patients accrued
- Distributions of important pretreatment and prognostic baseline variables
- The frequencies and severity of adverse events by treatment arm
- Compliance rates of treatment delivery

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, DFS, or any secondary endpoints, with the exception of reporting of adverse events.

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

13.5.4 Significance Testing for Early Termination and/or Reporting

13.5.4.1 Unacceptable Toxicity
The addition of trastuzumab to cisplatin and fluorouracil did not increase toxicity in the ToGA trial (Van Cutsem 2009). Furthermore, the addition of trastuzumab to cisplatin, paclitaxel, and radiation did not produce cardiac toxicity or increase any other toxicity. While it is unlikely that trastuzumab will increase the toxicity of chemoradiation, this will be carefully monitored, with a specific focus on the following adverse events:

- Grade 3/4 restrictive cardiomyopathy
- Patients with incipient CHF defined as an asymptomatic > 20% decrease in LVEF or a decrease of LVEF > 10% below the institutional lower limit of normal who are judged to require treatment according to institutional guidelines.

To address the safety of adding trastuzumab, the rate of the adverse events specified above will be reviewed after 25 and 50 patients have been entered on the trastuzumab arm and followed from the start of chemoradiation up to the earlier date of surgery or 6 weeks after completion of chemoradiation. The study chairs have determined that a rate of 20% or greater will be considered to be unacceptable. According to Fleming’s method with a maximum overall significance level of 0.05 if there are:

- 5 or more patients with cardiomyopathy-related events described above out of the first 25 evaluable patients, or
- 6 or more patients with cardiomyopathy-related events described above out of the first 50 evaluable patients

then the study will have exceeded the limit for unacceptable cardiomyopathy (Fleming 1982). If the number of unacceptable cardiomyopathy events crosses a boundary, as described in the rules above, then the conclusion will be that the treatment-related cardiomyopathy rate is greater than 20%. If this circumstance occurs, the study chairs, the RTOG gastrointestinal cancer committee chair, and the study statistician will review the adverse event data and make appropriate recommendations to the RTOG data monitoring committee (DMC) to consider when they review the toxicity results. These stopping rules provide 95% power for concluding that the rate of adverse events specified above exceeds 20%, when in fact that is the true rate.

13.5.4.2 Early Evaluation of Adverse Events Between Treatment Arms
After 50 evaluable patients have been entered and followed from the start of chemoradiation up to the earlier date of surgery or 6 weeks after completion of chemoradiation, an evaluation of adverse events will be performed, specifically including the group of adverse events listed in Section 13.5.4.1, all grade 3+ nonhematologic adverse events, and all grade 3+ adverse events.

13.5.4.3 Primary Endpoint: Disease-Free survival (DFS)
Three interim significance tests of treatment difference are planned. The timing of the interim analyses will be based on DFS failure events, as described in Section 13.1.1. The maximum number of events required for the study is 121. Under the alternative hypothesis that the addition of trastuzumab will increase median DFS from 15 months to 27 months, the
projected numbers of events and the nominal significance levels for rejecting the H₀ or the H₁ for each of these two interim analyses are shown in the table below:

<table>
<thead>
<tr>
<th>Interim Analysis</th>
<th>Efficacy: Reject H₀ if p (H₀) ≤</th>
<th>Futility: Reject H₁ if p (H₁) ≤</th>
<th># Events (Control Arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>≤ 0.001</td>
<td>0.005</td>
<td>61</td>
</tr>
<tr>
<td>#2</td>
<td>≤ 0.001</td>
<td>0.005</td>
<td>91</td>
</tr>
</tbody>
</table>

At each planned interim analysis, the p-value from the log-rank test assessing treatment efficacy and futility with respect to DFS will be compared to the nominal significance levels in the table above. If the computed p-value is less than or equal to the nominal significance level boundary for rejecting the H₀ (efficacy), then accrual to the trial will be stopped (if applicable), it will be concluded that the DFS with trastuzumab (Arm 2) is significantly higher than without trastuzumab (Arm 1) and the results will be reported. If the p-value is greater than or equal to the nominal significance level boundary for rejecting the H₁ (futility), then accrual to the trial will be stopped (if applicable) and it will be reported that it cannot be concluded that the DFS with trastuzumab (Arm 2) is significantly higher than without trastuzumab (Arm 1). Otherwise, if the one-sided p-value falls between the nominal significance levels for rejecting the H₀ and the H₁, accrual to the trial or follow-up (as applicable) will continue until the next interim or final analysis.

In addition to accrual, distributions of pretreatment characteristics, frequency and severity of adverse events, and compliance with protocol treatment, blinded efficacy results will be reported to the RTOG data monitoring committee (DMC), following the required number of events for each planned interim analysis.

### 13.5.5 Analysis for Endpoints Related to HRQOL

- **Distributions of QOL data collection patterns over all collection points in each treatment arm will be described.**
- **To inspect the missing data mechanism for each tool, at least a graphical method will be used.** A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples.

If the missing data is MCAR, listwise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data.

If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline QOL score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method such as multiple imputation will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism (Donaldson 2005) and then an imputation method such as multiple imputation will be applied. All results from the imputed analysis using the multiple imputation will be compared to the complete case analysis results to assess any potential biases.

### 13.5.5.1 FACT-E Scoring and Analysis

**13.5.5.1.1** The FACT-E will be scored per the FACT-E Scoring Guidelines (Version 4 [www.facit.org](http://www.facit.org)), with higher scores indicating better QOL.

**13.5.5.1.2** The primary objective in the HRQOL analysis is improvement in the FACT-E Esophageal Cancer Subscale (ECS) score, defined as an increase of 5 points or more from baseline to the assessment at 6 to 8 weeks following chemoradiation with or without trastuzumab, at the time of restaging prior to surgical resection. Chi-squared tests will be used to test the null hypothesis that the proportion of patients categorized as "improved" will be the same for the 2 treatment arms, versus the alternative hypothesis that the proportion of patients categorized as "improved" is higher for the trastuzumab arm.
13.5.5.1.3 Improvement in the ECS score, as defined above, will also be compared between the treatment arms for changes from baseline to both 1 and 2 years with the same methodology as listed above.

13.5.5.1.4 Correlation between pathologic complete response (pCR) and improvement in ECS score from baseline to 6 to 8 weeks following chemoradiation will be evaluated with chi-squared tests.

13.5.5.1.5 Chi-squared tests will be used to determine if pCR is prognostic or predictive of ECS score at 1 and/or 2 years.

13.5.5.1.6 The definition of improvement for both the Swallowing Index and Eating Index Subscale scores are defined as an increase of 2 or more points from baseline. Analyses similar to the ones described above for ECS scores will be done for the Swallowing and Eating Index scores.

13.5.5.2 EQ-5D Scoring and Analysis

13.5.5.2.1 The quality-adjusted survival of each treatment will be evaluated and compared using EQ-5D if the primary endpoint supports the primary hypothesis.

13.5.5.2.2 The EQ-5D is a 2-part self-assessment questionnaire. The first part consists of 5 items covering 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point likert scale (1-no problems, 2-moderate problems, and 3-extreme problems). The second part is a visual analog scale (VAS) valuing the current health state measured by a 100-point scale with a 10-point interval (0-worst imaginable health state, 100-best imaginable health state). We will transform the 5-item index score and VAS score into a utility score between 0 (worst health state) and 1 (best health state) for comparative purposes. Patients will complete the EQ-5D at the following time points: pretreatment (baseline), at 1 year from the start of treatment, and at 2 years from the start of treatment.

13.5.5.2.3 To examine trade-offs between the survival time and QOL, they will be combined for each patient into a single measurement: quality-adjusted life years (QALY). If (and only if) the primary endpoint hypothesis is substantiated, a quality-adjusted survival analysis will be conducted. The quality-adjusted survival analysis will not be done until after the primary endpoint results are published. QALY is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. QALY will be analyzed at 2 time points: at 1 year and 2 years from start of treatment, using the EQ-5D.

13.5.6 Analysis for Reporting the Initial Treatment Results

The primary hypothesis of this study is that the addition of trastuzumab during preoperative chemoradiation and for 12 months of maintenance following surgery will increase the median DFS from 15 months to 27 months, for HER2 positive patients with esophageal adenocarcinoma. This major analysis will occur after at least 121 DFS failure events have been observed, unless an early stopping rule is satisfied. It will include:

- Tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- Distributions of important prognostic baseline variables
- The frequencies and severity of adverse events by treatment arm.
- Compliance rate of treatment delivery
- Observed results with respect to the primary and secondary endpoints

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit will be tested using the log-rank statistic with a significance level of 0.05, given that the 2 interim analyses were carried out per Section 13.5.4.3. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factor included as a fixed covariate, as well as any factors that show an imbalance between the arms (eg, age, gender, race, Karnofsky performance status, etc.).

13.6 Gender and Minorities

Both men and women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, possible interaction between race/ethnicity and treatment have been considered. Based on RTOG studies 9405 and 0113, it is projected that
72% of the patients will be men and 28% women; 3% will be of Hispanic or Latino ethnicity and 97% will not; racial distribution will be 73% white, 26% black or African American, and 1% Asian. Assuming no differences between the ethnicities, or among the races, the statistical power for detecting the hypothesized treatment difference is 78% for males and 40% for females. Assuming no differences between genders or the ethnicities, the statistical power is 79% for whites and 37% for Blacks/African-Americans. The projected non-White/Black accrual rate is too low for any meaningful treatment comparisons. Assuming no differences between the genders, or among the races, the statistical power for detecting the hypothesized treatment difference in non-Hispanic/Latino ethnicity will be 88%. The projected Hispanic/Latino accrual rate is too low for any meaningful treatment comparisons.

The following table lists the projected accrual by gender, ethnic, and racial categories.

### Projected Distribution of Gender and Minorities

| Ethnic Category: Total of all subjects | Gender | | | |
|---------------------------------------|--------|--------|--------|
| Females | Males | Total |
| Hispanic or Latino | 1 | 4 | 5 |
| Not Hispanic or Latino | 44 | 111 | 155 |

| Ethnic Category: Total of all subjects | Gender | | | |
|---------------------------------------|--------|--------|--------|
| Females | Males | Total |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Asian | 1 | 1 | 2 |
| Black or African American | 11 | 30 | 41 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 33 | 84 | 117 |

| Racial Category: Total of all subjects | Gender | | | |
|---------------------------------------|--------|--------|--------|
| Females | Males | Total |
| 45 | 115 | 160 |
REFERENCES


Slamon, D, Eiermann, W, Robert, N, et al. BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2neu positive early breast cancer patients [abstract]. Data presented at the 29th Annual San Antonio Breast Cancer Symposium, December 16, 2006; San Antonio, Tx.


APPENDIX I
Informed Consent Template for Cancer Treatment Trials (NCI Template Date: August 2009)
(English Language)

RTOG 1010

A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma

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 cancer of the esophagus (esophageal adenocarcinoma).

A standard treatment for esophageal adenocarcinoma is treatment with radiation therapy and the chemotherapy drugs paclitaxel and carboplatin. Afterwards surgery is done to remove the cancer by removing the esophagus. This study will test whether the addition of the drug trastuzumab to standard treatment with paclitaxel, carboplatin, and surgery can help prevent your cancer from growing back.

Trastuzumab is a drug that can only be effective in cancers that are HER2 positive. HER2 positive cancer means that the cancer has increased amounts of either HER2 genes or HER2 protein. (Genes are inside cells and make proteins.) Trastuzumab attaches to the HER2 protein. In patients with HER2 positive breast cancer, trastuzumab is proven to reduce cancer from growing back. However, the use of trastuzumab for esophageal cancer is experimental.

Why is this study being done?
This study is being done to compare the effects, good and/or bad, of the addition of trastuzumab to standard chemotherapy, radiation, and surgery for patients with HER2 positive esophageal cancer.

How many people will take part in the study?
About 480 patients will have their esophageal cancer tissue tested to see if it is HER2 positive. It is expected that about 1 in 3 patients have esophageal cancer that is HER2 positive and therefore, about 160 patients with HER2 positive cancer will take part in the treatment portion of the study.

What will happen if I participate in this part of the research study?

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.
• HER 2 Testing
Your study doctor will need to send some of your tumor tissue (obtained by an endoscopy) to a central office. There, a pathologist will determine if your cancer is HER2 positive. This tissue submission for review is required for this study.

Endoscopy with biopsy: during an endoscopy, your study doctor will insert a tube into your throat that will allow him/her to look at your esophagus. Your study doctor will remove some of the cancerous tissue (biopsy) during this procedure.

If there is not enough tumor tissue present to perform the HER2 test or if your cancer is found to be HER2 negative, you will not be able to continue on the study and you will not receive treatment for your cancer on the study. You will talk to your doctor about what treatment for your cancer is best for you.

In addition to HER2 testing, you will need to have the following additional 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.

• Evaluation of your ability to carry out daily activities
• CT scan of your chest, abdomen and pelvis (A CT scan is a computerized image that uses x-rays to look at one part of your body) OR Whole-body PET/CT scan (A PET scan is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar [glucose] combined with a low-dose radioactive substance [a tracer]. A camera records the tracer’s signal as it travels through your body.)
• Bronchoscopy: A test in which a small scope is put into your trachea (airway) that enables your doctor to look directly inside the trachea. If the endoscopy or CT scan showed that your esophageal cancer is close to your trachea a bronchoscopy is done to see if the esophageal cancer is growing inside the trachea.
• Blood tests (about 2-3 teaspoons of blood will be taken from your vein)
• For women able to have children, a blood or urine pregnancy test

If your cancer is found to be HER2 positive and the other exams, tests, and procedures indicate you can potentially receive treatment on study, you will need to have the following additional exams, tests, or procedures to find out if you continue to the treatment portion of 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.

• Physical examination by several doctors
• Recording of your weight
• Evaluation of your ability to carry out daily activities
• Whole-body PET/CT scan if one wasn’t already done in conjunction with this study
• EKG (electrocardiogram): a test of your heart function
• Echocardiogram or MUGA scan: to measure your heart function
• Endoscopic ultrasound: a procedure in which the size of your cancer can be accurately measured; your study doctor may remove some of the cancerous tissue
(biopsy) during this procedure. (An endoscopic ultrasound does not need to be done if your CT or PET/CT scan show that you have suspicious lymph nodes)

- For women able to have children, a blood pregnancy test

You will also be asked to report any use of over-the-counter or herbal products to your study doctor, so that he or she can make sure you are not taking any products that interact with any of the study drugs.

Eligible participants will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in each group.

Radiation: All patients will receive radiation. Radiation treatment will be given once a day, 5 days a week, for 5 and a half weeks (28 treatments). All radiation treatments will be given to you as an outpatient.

Chemotherapy: All patients will also receive chemotherapy with paclitaxel and carboplatin. Starting the same day as your radiation treatments, you will receive paclitaxel and carboplatin once a week for 6 weeks (6 cycles). Paclitaxel and carboplatin will be injected into a vein (intravenously). You will be given intravenous fluids and medicines to prevent nausea. You will also be given diphenhydramine, ranitidine, and dexamethasone to prevent an allergic reaction. Your chemotherapy treatments will be given as an outpatient at your institution. The treatment will last for about 3 and a half hours, once a week.

If you are in group 1 (often called "Arm 1"): You will also receive the drug trastuzumab. Starting the same day as your first dose of radiation, paclitaxel, and carboplatin, you will be given trastuzumab by vein as an outpatient over 90 minutes. You will receive trastuzumab weekly, over 30-90 minutes, for a total of 6 doses until the radiation treatment is completed, on days 1, 8, 15, 22, 29, and 36. Then 3 weeks later, on day 57, you will have 1 additional treatment of trastuzumab prior to surgery. As soon as you have adequately recovered from surgery to remove your esophagus, you will receive trastuzumab every 3 weeks for 13 treatments (over about 10 months).

If you are in group 2 (often called "Arm 2"): You will not receive trastuzumab. You will be treated with radiation paclitaxel, and carboplatin.

Surgery: All patients in this study will have a biopsy of the tumor 4-6 weeks after the last dose of radiation. Patients with no metastatic disease will have surgery to remove the esophagus about 5-8 weeks after the last dose of radiation. Patients with metastatic disease will not receive additional protocol treatment.

Exams, Tests, and Procedures:

For all patients, during the paclitaxel, carboplatin, and radiation:
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

**Every week:**
- Physical examination
- Recording of your weight
- Evaluation of your ability to carry out daily activities
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects you may be experiencing

**For all patients, when you are finished receiving radiation, paclitaxel, and carboplatin, prior to having surgery:**
You will need to have the following exams, tests, and procedures. They are being done to see how the treatment you received affected you and your cancer.

**At the end of paclitaxel, carboplatin, and radiation**
- Physical examination
- Recording of your weight
- Echocardiogram or MUGA scan (to measure your heart function)
- CT scan of your chest, abdomen, and pelvis OR whole-body PET/CT scan
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)
- Evaluation of your ability to carry out daily activities
- Evaluation of any side effects you may be experiencing
- Endoscopy with biopsy

**Every 4 months after surgery for 2 years, then yearly**
- Physical examination
- Recording of your weight
- CT scan of your chest, abdomen, and pelvis or a PET/CT scan
- Evaluation of your ability to carry out daily activities
- Evaluation of any side effects you may be experiencing

**For Group 1 patients only: 3, 6, 9, and 12 months after endoscopy**
- Echocardiogram or MUGA scan (to measure your heart function)

**For Group 2 patients only: 6 and 12 months after endoscopy**
- Echocardiogram or MUGA scan (to measure your heart function)

**For Group 1 patients only, every 6 weeks during trastuzumab (after surgery)**
- Physical examination and recording of your weight
Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

Patients without HER2 Positive Cancer
Discuss treatment options with doctor

Patients with HER2 Positive Cancer
Randomize

Group 1
Daily radiation, M-F, for 5 ½ weeks
Paclitaxel and carboplatin, once a week for 6 weeks on days 1, 8, 15, 22, 29, and 36.
Trastuzumab, days 1, 8, 15, 22, 29, 36, and 57.

Group 2
Daily radiation, M-F, for 5 ½ weeks
Paclitaxel and carboplatin, once a week for 6 weeks on days 1, 8, 15, 22, 29, and 36.

Biopsy and Required Submission of Tissue for HER2 Testing

Surgery
5-8 weeks after completion of radiation

Group 1
Trastuzumab, every 3 weeks for 13 treatments (about 10 months)

Group 2

How long will I be in the study?

Patients in group 1: You will receive paclitaxel, carboplatin, trastuzumab, and radiation for about 5 ½ weeks. Then about 5-8 weeks after treatment, you will have surgery. After surgery, you will receive trastuzumab every 3 weeks for about 10 months. Your study doctor will ask you to visit the office for follow-up exams every 4 months for 2 years, then yearly for your lifetime.

Patients in group 2: You will receive paclitaxel, carboplatin, and radiation for about 5 ½ weeks. Then about 5-8 weeks after treatment, you will have surgery. Your study doctor will ask you to visit the office for follow-up exams every 4 months for 2 years then yearly for your lifetime.
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 tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so he/she can evaluate any risks from the treatment. Another reason to tell your study 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?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don’t know all the side effects that may happen. Side effects may be mild or very serious. Your doctor may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the treatment. 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 related to the radiation include those that are:

**Likely**
- Inflammation of the esophagus
- Narrowing of the esophagus, which can cause problems with swallowing
- Fatigue
- Decrease in blood counts, which can cause infection, bleeding, and bruising
- Tanning and redness of the skin in the treatment area
- Nausea/vomiting

**Less Likely**
- Growth of fibrous tissues underneath your skin
- Diarrhea
- Weight loss

**Rare but Serious**
- Inflammation of the muscle tissue of the heart
- Inflammation and/or scarring of the lung tissue
- Bleeding for the esophagus and stomach

Risks and side effects related to paclitaxel include those that are:
** Likely

- Fatigue
- Hair loss
- Nausea
- Vomiting
- Diarrhea
- Abdominal pain
- Decrease in blood counts, which can cause infection, (white blood cell count) or bleeding or bruising (platelet count)
- Anemia (decrease in red blood cell count)
- Tanning and redness of the skin in the treatment area
- Hardening or tenderness of the skin in the treatment area

** Less Likely

- Mouth sores
- Tingling or numbness in your hands and feet, which may be long term or permanent
- Stiffness or pain in your joints and muscles
- Ulceration of the skin at the injection site, including redness, tenderness, swelling, and cellulitis (infection of the skin)
- Inflammation of the liver with a rise in liver function tests
- Tearing of the eyes
- Inflammation of the lining of the eye
- Low blood pressure
- Slowing of the heart rate
- Premature heart beats
- Changes in skin or nail color
- Fragility of nails
- Swelling of the legs or ankles
- Constipation

** Rare but Serious

- Problems with your heart, including irregular or rapid heart beat, high blood pressure, and fainting
- Heart attack
- Congestive heart failure (heart muscle weakness, swelling, and shortness of breath)
- Blood clots in the veins
- Severe allergic reaction with low blood pressure, shortness of breath, rash, swelling of the face, redness in the face, chest pain, and shock
- Death from allergic reaction
- Death from infection due to low white blood cell count, including sepsis (blood infection), peritonitis (infection of the stomach lining), and pneumonia
- Visual changes including flashes of light
- Hearing loss
- Muscle weakness
- Liver failure
- Intestinal obstruction
• Intestinal perforation
• Pancreatitis (inflammation of the pancreas)
• Ischemic colitis (impaired blood flow to the bowel)
• Lung inflammation or fibrosis (hardening of tissue)
• Pulmonary embolism (blood clot in lung)
• Seizure
• Balance or coordination difficulty

Risks and side effects related to carboplatin include those that are:

**Likely**
- Decrease in blood counts, which can cause infection, (white blood cell count) or bleeding or bruising (platelet count)
- Anemia (decrease in red blood cell count)
- Nausea
- Vomiting
- Diarrhea
- Loss of appetite and taste
- Fatigue
- Weight loss
- Hair loss

**Less Likely**
- Mouth sores
- Restlessness
- Tingling or numbness in your hands and feet, which may be long term or permanent
- Muscle cramps
- Weakness
- Hiccups
- Increase in blood uric acid level
- Inflammation of the liver resulting in rise in liver function tests
- Blurred vision
- Changes in body calcium, potassium, sodium, phosphate, and magnesium levels, which can cause muscle cramps, weakness, and abnormal heart rhythms

**Rare but Serious**
- Leukemia (another type of cancer that is likely to be fatal)
- Involuntary movements, loss of coordination, and seizures
- Severe allergic reaction with low blood pressure, shortness of breath, rash, swelling of the face, chest pain, and shock
- Damage to the ears, including hearing loss and ringing in the ears
- Kidney failure
- Death from allergic reaction
- Death from infection due to low white blood cell count
- Heart attack
- Stroke
- Irregular heart beat
• Blindness

Risks and side effects related to trastuzumab include those that are:

**Less Likely**

- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- A condition in which the heart muscle is abnormally enlarged or thickened
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Fluid in the sac around the heart
- Inflammation (swelling and redness) of the sac around the heart
- Fast heartbeat; regular rhythm
- Fast heartbeat usually originating in an area located above the ventricles
- Belly pain
- Diarrhea
- Irritation or sores in the lining of the mouth
- Nausea or the urge to vomit
- Vomiting
- Chills
- Fatigue or tiredness
- Fever
- Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Chest pain not heart-related
- Pain
- Reaction during the infusion of a drug which may be life-threatening and may result in low blood pressure, fever, chills, difficulty breathing and kidney damage
- Infection
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Increased blood level of a liver enzyme (GGT)
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Back pain
- Bone pain
- Muscle pain
- Pain in the area of the tumor
- Headache or head pain
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
• Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs
• Stuffy or runny nose, sneezing
• Sudden constriction of the muscles in the walls of the bronchioles (small airways of the lung)
• Cough
• Shortness of breath
• Decrease in the oxygen supply to a tissue
• Build up of a large amount of fluid between the layers of tissue that line the lungs and chest cavity
• Inflammation (swelling and redness) of the lungs
• Acne
• Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
• Hives
• High blood pressure
• Low blood pressure

**Rare but Serious**

• Abnormal reaction of the body to substances, called allergens, that are contacted through the skin, inhaled into the lungs, swallowed, or injected (allergic reaction)
• Serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness
• Abnormal build up of fluid in the lungs
• Scarring of the lungs that can cause shortness of breath and interfere with breathing

**Risks and side effects related to surgery include those that are:**

**Likely**

• Abnormal heart rhythm, which could cause irregular and/or forceful beating of the heart (palpitations) and/or decreased blood pressure
• Incomplete expansion of the lungs (atelectasis) with retention of secretions and shortness of breath

**Rare but Serious**

• Bleeding during the operation from a blood vessel, which may require a blood transfusion
• Infection of the operative wound, which may require that the incision be reopened and packed with gauze
• A blood clot in the lungs, which could result in shortness of breath
• Fluid in the lungs, which could result in shortness of breath and rapid breathing
• Pneumonia, which could require you to go back on a ventilator
• A leak from the thoracic duct (a lymph vessel) that can be damaged during surgery, which could result in fluid around the lungs, shortness of breath, and loss of protein leading to malnutrition
• A leak where the end of the esophagus and stomach are reattached, which could result in fever, increased white cell count, and low blood pressure. Drainage of
the leak could be required.

- Scar tissue that can cause the area where the end of the esophagus and stomach or colon are attached to close up. This could lead to difficulty swallowing and require dilation.
- Death

**Risk of secondary leukemia or other cancers:** In very rare cases, acute leukemia or other cancers may develop after treatment with paclitaxel, carboplatin, radiation and trastuzumab.

**Reproductive risks:** The drugs in this study can affect an unborn baby. You should therefore not become pregnant or father a baby while on this study and for at least 60 days after the last of chemotherapy and/or trastuzumab. Women who are able to have children will be required to have a pregnancy test before taking part in this study. Women should not breastfeed a baby while on this study and, if you are receiving trastuzumab, for at least 60 days after the last trastuzumab dose. It is important that 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.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. While researchers hope that the addition of trastuzumab to the standard treatment of radiation therapy, chemotherapy, surgery will be more effective against esophageal cancer compared to standard treatment without trastuzumab, there is no proof of this yet. We do know that the information from this study will help researchers learn more about this therapy combination as a treatment for cancer. This information could help future cancer patients.

**What other choices do I have if I do not take part 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 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 study doctor about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**
Data are housed at RTOG Headquarters in a password-protected database. 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)
- The American College of Surgeons Oncology Group (ACOSOG)
- The Southwest Oncology Group (SWOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Qualified representatives of pharmaceutical collaborators, manufacturers and distributors of trastuzumab
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide patients and doctors greater access to cancer trials [for patients enrolled via CTSU]

**What are the costs of taking part in this study?**

You and/or your health plan/insurance company will need to pay for some or all 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.

Genentech and the NCI are supplying trastuzumab at no charge while you take part in this study. However, you or your health plan may need to pay for costs of the supplies for the administration of the trastuzumab. You and/or your health plan/insurance company will need to pay for your treatment with paclitaxel and carboplatin.

The cost of the MUGA scans required if you are taking trastuzumab may or may not be covered by your health plan/insurance company. It is recommended that you check with your health plan/insurance company prior to receiving the first MUGA scan to determine whether coverage is provided.

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

Even though it probably won’t happen, it is possible that the manufacturer may not continue to provide the trastuzumab to the NCI for some reason. If a problem with getting trastuzumab occurs, your study doctor will talk to you about it.

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](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 study 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 take part 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.

A Data Monitoring Committee (DMC) will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

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

You can say “yes” or “no” to the following studies. Below, please mark your choice for each question.

**Quality of Life Study**

We want to know your view of how your life has been affected by cancer and its treatment. This “Quality of Life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete two questionnaires at the following times: before you begin treatment, after you finish chemotherapy and radiation but prior to surgery, and at 1 and 2 years after you start treatment. It takes about 10 minutes to fill out each of the questionnaires.

If any questions make you feel uncomfortable, talk with your study doctor or nurse about skipping those questions and not giving an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the questionnaires. You may change your mind about participating at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

**Please circle your answer.**

I choose to take part in the quality of life study. I agree to fill out the 2 quality of life questionnaires.

YES    NO

**About Using Tissue, Blood, and Urine for Research**

You are going to have a biopsy, and your tissue will be sent a central office to determine if your cancer is HER2 positive.
We would like to keep some of the tissue that is left over for future research. In addition to the tumor tissue, if your cancer is HER2 positive, we would like to collect 3 teaspoons of your blood and 5 teaspoons of your urine. Blood and urine for research will be collected twice, before you start treatment and after you finish chemotherapy and radiation but prior to surgery.

If you have surgery to remove your esophagus while you are on the study, we would also like to keep some of the left over tumor tissue for future research.

If you agree, your tissue, blood, and urine will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available at the following web site: http://www.rtog.org/tissue%20for%20research_patient.pdf

The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue, blood, and urine will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

**Things to Think About**

The choice to let us keep the left over tissue and your blood and urine for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue, blood, and urine 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 and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the doctor/institution 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, blood, and urine are 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, blood, and urine will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new treatments for cancer and other diseases in the future.

**Benefits**

The benefits of research using tissue include learning more about what causes cancer 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 records. 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 each sentence below and think about your choice. After reading each 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 decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue □Yes □ No
   - Blood □Yes □ No
   - Urine □Yes □ No

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
   - Tissue □Yes □ No
   - Blood □Yes □ No
   - Urine □Yes □ No

3. Someone may contact me in the future to ask me to take part in more research.
   □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 ________________________________

Date ________________________________
## APPENDIX II: STUDY PARAMETER TABLE

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Treatment</th>
<th>During Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologically confirmed diagnosis</td>
<td>Prior to Step 1 registration but must be within 56 days prior to Step 2 registration</td>
<td>Within 56 days prior to Step 2 registration</td>
<td></td>
</tr>
<tr>
<td>Endoscopy w/ biopsy</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopic ultrasound</td>
<td>Pts not exhibiting adenopathy on CT or whole-body PET/CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Determination of HER2 status by central laboratory</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>History/physical w/ weight</td>
<td></td>
<td>X X X</td>
<td>Arm 1: Every 6 wks during maintenance trastuzumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm 2: Every 4 months for 2 years then annually</td>
</tr>
<tr>
<td>Chest/abdominal/pelvic CT or whole-body PET/CT</td>
<td>X</td>
<td>X*</td>
<td>X X</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td></td>
<td></td>
<td>Arm 1: Every 6 wks during maintenance trastuzumab</td>
</tr>
<tr>
<td>EKG</td>
<td></td>
<td></td>
<td>Med/Rad Onc, Surg Eval</td>
</tr>
<tr>
<td>Med/Rad Onc, Surg Eval</td>
<td></td>
<td></td>
<td>X X</td>
</tr>
</tbody>
</table>

*Continued on next page*
### APPENDIX II (Continued)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Treatment</th>
<th>During Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiogram or MUGA for LVEF</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>CBC w/ diff, ANC, platelets, Hgb</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Na, K, BUN, Creatinine, Glucose</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Bilirubin, AST</strong></td>
<td>X</td>
<td>X</td>
<td>Every 2 wks X</td>
</tr>
<tr>
<td><strong>Pregnancy test (if applicable)</strong></td>
<td>Urine or serum</td>
<td>Serum</td>
<td>X</td>
</tr>
<tr>
<td><strong>Arterial blood gas</strong></td>
<td>Recommended</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>PFTs</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Plasma/urine for banking, if patient consents (HER2+ patients only)</strong></td>
<td>Before treatment start</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Whole blood for banking, if patient consents (HER2+ patients only)</strong></td>
<td>Before treatment start (or at any other visit during or after treatment)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
APPENDIX II (Continued)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Treatment</th>
<th>During Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior to Step 1 registration but must be within 56 days prior to Step 2 registration</td>
<td>Within 56 days prior to Step 2 registration</td>
<td>Every wk during chemo/RT</td>
</tr>
<tr>
<td>Tissue for banking, if patient consents (HER2+ patients only)</td>
<td>Collected from diagnostic biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACT-E, if patient consents</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>EQ-5D, if patient consents</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* See Section 3.0 for details and exceptions.
APPENDIX III

ZUBROD PERFORMANCE SCALE

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

Primary Tumor (T)*

TX  Primary tumor cannot be assessed
T0  No evidence of primary tumor
Tis  High-grade dysplasia**
T1  Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a Tumor invades lamina propria or muscularis mucosae
T1b Tumor invades submucosa
T2  Tumor invades muscularis propria
T3  Tumor invades adventitia
T4  Tumor invades adjacent structures
T4a Resectable tumor invading pleura, pericardium, or diaphragm
T4b Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

* 1) At least maximal dimension of the tumor must be recorded and 2) multiple tumors require the T(m) suffix.

**High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Regional Lymph Nodes (N)*

NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in 1-2 regional lymph nodes
N2  Metastasis in 3-6 regional lymph nodes
N3  Metastasis in ≥ 7 regional lymph nodes

*Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis.

Distant Metastasis (M)

M0  No distant metastasis
M1  Distant metastasis
APPENDIX IV (Continued)

AJCC STAGING SYSTEM

ESOPHAGUS and ESOPHAGEAL JUNCTION

ANATOMIC STAGE/PROGNOSTIC GROUPS

### Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Grade</th>
<th>Tumor Location**</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>1, X</td>
<td>Any</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1, X</td>
<td>Any</td>
</tr>
<tr>
<td>IB</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>2-3</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T2-3</td>
<td>N0</td>
<td>M0</td>
<td>1, X</td>
<td>Lower, X</td>
</tr>
<tr>
<td>IIA</td>
<td>T2-3</td>
<td>N0</td>
<td>M0</td>
<td>1, X</td>
<td>Upper, middle</td>
</tr>
<tr>
<td></td>
<td>T2-3</td>
<td>N0</td>
<td>M0</td>
<td>2-3</td>
<td>Lower, X</td>
</tr>
<tr>
<td>IIB</td>
<td>T2-3</td>
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<td>M0</td>
<td>2-3</td>
<td>Upper, middle</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2</td>
<td>N2</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4a</td>
<td>N1-2</td>
<td>M0</td>
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<td>Any</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
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<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>N3</td>
<td>M0</td>
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<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

**Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus.

### Adenocarcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>1, X</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1-2, X</td>
</tr>
<tr>
<td>IB</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>1-2, X</td>
</tr>
<tr>
<td>IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
</tr>
<tr>
<td>IIIC</td>
<td>T1-2</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2</td>
<td>N2</td>
<td>M0</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td>Any</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4a</td>
<td>N1-2</td>
<td>M0</td>
<td>Any</td>
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<tr>
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APPENDIX V
Pathology Assessment of the Surgical Specimen

The entire esophageal specimen and lymph nodes will be submitted for local pathological review.

The gross appearance of treated tumor varies from mucosal ulceration to a fibrous scar or a prominent mass lesion in the case of a less than profound tumor regression. The ulcerated or scarred gross lesions should be blocked and sequentially and entirely submitted for histopathologic evaluation (approximately 3 mm in thickness). One section from each block should be evaluated by hematoxylin and eosin (H&E) staining. If gross tumor is present and large (> 5cm), representative sections of the tumor may be evaluated.

Pathologic complete response is defined as no viable residual tumor cells. Acellular residual mucin pools should be noted but also considered pathologic complete response.

Down-staging will be determined by comparing pre-radiation clinical staging (CT scan, PET scan and EUS) to the pathologic size and stage (both tumor and nodal staging). Residual tumor grading will be per Wu (2007). See diagram below:

APPENDIX VI

RTOG BIOSPECIMEN COLLECTION INSTRUCTIONS
RTOG FFPE PLUG KIT INSTRUCTIONS
RTOG BLOOD COLLECTION KIT INSTRUCTIONS
RTOG URINE COLLECTION KIT INSTRUCTIONS

Shipping Instructions:

US Postal Service Mailing Address: For FFPE or 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 or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223,
San Francisco, CA 94115

- Include all RTOG paperwork in pocket of biohazard bag.
- Check that the STF has the consent boxes checked off.
- Check that all samples are labeled with RTOG study and case number, and include date of collection as well as collection time point.

- FFPE Specimens:
  - Slides should be shipped in a plastic slide holder/ slide box. Place a small wad of padding in top of container if you can hear the slides shaking they are likely to break during shipping.
  - FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear them shaking they are likely to break during shipping.
  - Slides, Blocks or Plugs can be shipped ambient or with a cold pack either by USPS to the USPS address (94143) or by Courier to the Street Address (94115). Do NOT ship on Dry Ice.

- Frozen Specimens:
  - Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80C until ready to ship.

- For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by email at: RTOG@ucsf.edu or (415)-476-7864 or fax (415)-476-5271
RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

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

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label punch tool with proper specimen ID. DON’T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or email us if you have any questions or need additional specimen plug kits.

Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

*NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship: Specimen plug kit, specimen in punch tool, and all paperwork to the address below:

☐ For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the RTOG Biospecimen Resource by email at: RTOG@ucsf.edu or call 415-476-RTOG(7864) /FAX 476-5271;

US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource at UCSF
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Trackable FFPE shipments
RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of plasma as specified in protocol.

**Kit contents:**
- One Purple Top EDTA tube #1 for plasma (A)
- One Purple Top EDTA tube #2 for Whole Blood (B)
- Twenty (20) 1 ml cryovials
- Specimen Transmittal Form
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Kit Instructions
- UN1845 DRY Ice Sticker
- UN3373 Biological Substance Category B Stickers
- Biohazard bags (3)
- Absorbent shipping material (3)

**Preparation and Processing of Plasma**

**A) Plasma: Purple Top EDTA tube #1**

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

  **Process:**
  1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
  2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
  3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
  4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (up to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
  5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
  6. Store frozen plasma -70 to -90°C until ready to ship on dry ice.
  7. See below for storage conditions.

  **PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on STF.**

**B) Whole Blood For DNA: Purple Top EDTA tube #2**

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

  **Process:**
  1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
  2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (up to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “blood”.
  3. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C.
  4. Store blood samples frozen -70 to -90°C until ready to ship on dry ice.
  5. See below for storage conditions.

  **PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on STF.**

**Storage and Shipping:**

**Freezing and Storage:**

- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
Store at –80°C (-70°C to -90°C) until ready to ship.

If a -80°C Freezer is not available,

- Samples can be stored short term in a -20°C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).
- OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).
- OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only- Canada Mon-Tues).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

**Shipping/Mailing:**

- Ship specimens on Dry Ice overnight *Monday-Wednesday (Monday-Tuesday from Canada)* to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.

**RTOG BLOOD COLLECTION KIT INSTRUCTIONS**

- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice breaking the tubes.
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.*
- For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271

**Shipping Address : FedEx/UPS/Courier address (For all frozen samples)**

RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115

Contact Phone 415.476.7864
RTOG URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of Urine Specimens

Kit Contents:
- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipets
- Absorbent Paper Towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:
- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/ cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimens as "urine".
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C Freezer until ready to ship

Storage and Shipping:

Freezing and Storage
- Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at –20°C or 80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).
OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:
- Ship specimens on Dry Ice overnight Monday-Wednesday (Monday-Tuesday from Canada) to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice breaking the tubes.
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.
- For questions regarding ordering, collection, or shipping a Urine Collection Kit, please Email RTOG@ucsf.edu or call (415) 476-7864 or fax (415) 476-5271
Shipping Address: FedEx/UPS/Courier address (For all frozen samples)

RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115
Contact Phone 415.476.7864
APPENDIX VII
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 Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) 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 members’ area at https://www.ctsu.org

All forms and documents associated with this study can be downloaded from the RTOG 1010 Web page on the CTSU members’ area of the website (https://www.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS.

Requirements for RTOG 1010 site registration:
• CTSU IRB Certification
• CTSU IRB/Regulatory Approval Transmittal Sheet
• IRB Approved Consent
• 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 1010
• 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 pre-study evaluations performed within the time period specified in the protocol.
• Pathology materials for Central review of HER2 eligibility submitted per Section 10.2

CTSU Procedures for Patient Enrollment
1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon-Fri. 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
• Eligibility Checklist for Step 1

STEP 2
• CTSU Patient Enrollment Transmittal Form
• Eligibility Checklist for Step 2
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. 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 will 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 access the RTOG’s on-line registration system to register the patient. Tissue must be submitted for HER2 Central review for all patients registered to Step 1. HER2 negative patients will not proceed to Step 2. For HER2 positive patients, sites must contact the CTSU to register to Step 2. The CTSU registrar will access RTOG’s online registration system 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. Radiation therapy and protocol treatment must begin within 10 days after Step 2 registration, on a Monday or Tuesday if possible.

DATA SUBMISSION AND RECONCILIATION
1. All case report forms (CRFs) associated with this study must be downloaded from the RTOG 1010 Web page located on the CTSU members’ area of the website (https://www.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 directly to the RTOG unless an alternate location is specified in the protocol. Do not send study data to the CTSU.

3. The RTOG data center will query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the RTOG data center and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the RTOG data center.

SPECIAL MATERIALS OR SUBSTUDIES
1. Specimen collection for banking (Recommended. See protocol section 10.3)
   - Collect, prepare, and submit specimens as outlined in the protocol
   - Do not send specimens, supporting clinical reports, or transmittals to the CTSU

2. Quality of Life Assessments (Protocol section 11.4)
   - Submit completed forms as outlined in the protocol

SERIOUS ADVERSE EVENT (AE) REPORTING Section 7.8)
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 members’ side of the website (https://www.ctsu.org) or by drilling down to the Adverse Event Reporting Forms link under the documents folder of the RTOG 1010 Web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.
**DRUG PROCUREMENT** (Section 7.3)

Investigational agents: Trastuzumab supplied by Genentech

Commercial agents: Carboplatin; Paclitaxel

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

2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center tree on the RTOG 1010 Web page.