For Protocol Amendment 6 to: **RTOG 1010,** A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma

NCI/Local Protocol #: RTOG 1010

NCI Protocol Version Date: November 15, 2018

Section	Change
Global	• Formatting and typographical errors were corrected as needed. • The protocol version date was updated in the document footer.
Cover pages	Study Team Contact information for Lisa Kachnic, Lawrence P. Leichman, Heinz-Joseph Lenz, and Kathryn Winter were updated. Document History Table This amendment was added. CTSU Information • This table was updated per NCI required language. • The suite number for NRG Oncology's office address was updated from *"1600"* to *"1720".*
5.0 5.3.1	Revisions to these sections were made to reflect the most updated NCI required language.
7.10	Due to CTEP's migration from CTCAE v 4.0 to CTCAE v 5.0, the protocol was revised to reflect the following: • CTCAE v 4.0 will be utilized for AE reporting until March 31, 2018; • Beginning April 1, 2018, CTCAE version 5.0 will be utilized for CTEP-AERS reporting; • All study case report forms will continue to use CTCAE version 4.0.
12.0	The suite number for NRG Oncology's office address was updated from *"1600"* to *"1720".*

NRG ONCOLOGY

RTOG 1010

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

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

NRG Oncology Study Team (15-NOV-2018)
(Study Team continued on next page)

Principal Investigator/Medical Oncology
Howard Safran, MD
The Brown University Oncology Group
593 Eddy Street
Providence, RI 02903
401-444-6217/FAX 401-444-8417
hsafran@lifespan.org

Radiation Oncology Co-Chair
Theodore S. Hong, MD
Massachusetts General Hospital
100 Blossom St
Cox 3
Boston, MA 02114
617-724-1159/FAX 617-726-2603
tshong1@partners.org

Radiation Oncology Co-Chair
Michael Haddock, MD
Mayo Clinic
200 First St SW
Rochester, MN 55905
507-284-2669/FAX 507-284-0079
haddock.michael@mayo.edu

Quality of Life Co-Chair
Lisa Kachnic, MD
Radiation Oncology, Vanderbilt University Medical Center
2220 Pierce Avenue, B-1034A
Nashville, TN 37232
615-343-3523/Fax: 615-343-3075
lisa.a.kachnic@vumc.org

Correlative Science Co-Chair
Chandan Guha, MD, PhD
Department of Radiation Oncology
Montefiore Medical Center
Albert Einstein College of Medicine
111 East 210 Street
Bronx, NY 10467
718-920-2702/FAX 718-231-5064
cguha@montefiore.org

Translational Co-Chair
Ulrich Rodeck, MD, PhD
Thomas Jefferson University
233 S 10th Street; BLSB 409
Philadelphia, PA 19107
215-503-5622/FAX 215-503-5788
ulrich.rodeck@mail.jci.tju.edu

Pathology Co-Chair
Murray Resnick, MD, PhD
The Rhode Island Hospital
593 Eddy Street
Providence RI 02930
401-444-4380/FAX 401-444-8514
mresnick@lifespan.org

Senior Statistician
Kathryn Winter, MS
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19103
215-574-3198/ FAX 215-928-0153
winterk@nrgoncology.org

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

Study Team (Continued) (15-NOV-2018)

Medical Oncology Co-Chair/SWOG
Lawrence P. Leichman, MD
UC San Diego Moores Cancer Center
3855 Health Sciences Drive
Suite 0698
La Jolla, CA 92093 US
760-416-4860
lleichman@ucsd.edu

Correlative Science Co-Chair/SWOG
Heinz-Joseph Lenz, MD
University of Southern California
Norris Comprehensive Cancer Center
1441 Eastlake Avenue
NOR 3456
Los Angeles, CA 90033
323-865-3955/FAX 323-865-0061
lenz@usc.edu

Medical Oncology Co-Chair/ECOG-ACRIN
Lakshmi Rajdev, MD
Montefiore Medical Center
1825 Eastchester Road
Room 2, South 50
Bronx, NY 10461
718-904-2900/FAX:718-904-3892
lrajdev@montefiore.org

Medical Oncology Co-Chair/ NRG Oncology (formerly NSABP)
Michael J. Guarino, MD
NSABP Foundation, Inc.
Four Allegheny Center – 5th Floor
Pittsburgh, PA 15212-5234
412-330-4600/FAX: 412-330-4660
mguarino@cbg.org

Radiation Oncology Co-Chair/Alliance
Thomas Dipetrillo, MD
The Rhode Island Hospital
593 Eddy Street
Providence RI, 02903
401-444-8331/FAX 401-444-5335
tdipetrillo@lifespan.org

Thoracic Surgery Co-Chair/Alliance
Dennis Wigle, MD, PhD.
Mayo Clinic
200 First Street, SW
Rochester, MD 55905
507-284-8462/FAX 507-284-0058
Wigle.Dennis@mayo.edu

Protocol Agent

Agent	Supply	NSC #	IND #
Trastuzumab	NCI/PMB	**688097**	

Participating Sites

☐ U.S. Only
☐ Canada Only
☒ U.S. and Canada
☐ Approved International Member Sites

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

Document History

	Version/Update Date	Broadcast Date
Amendment 6	**November 15, 2018**	**N/A**
Amendment 5	June 13, 2016	June 27, 2016
Closure	-	November 9, 2015
Amendment 4	November 5, 2014	January 12, 2015
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Update	August 16, 2011	August 16, 2011
Amendment 1	July 26, 2011	August 16, 2011
Update	February 3, 2011	February 3, 2011
Activation	December 13, 2010	December 30, 2010

NRG Oncology
1-800-227-5463, ext. 4189

RTOG 1010

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

<table>
<tr><th colspan="3">CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (15-NOV-2018)</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.

Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com</td><td>Submit study data to:
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19103

Submit data electronically via the NRG Oncology/RTOG web site, www.rtog.org

Do <u>not</u> submit study data or forms to CTSU Data Operations. Do <u>not</u> copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' web site is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3">For clinical questions (i.e. patient eligibility or treatment-related): Contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3">For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical 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.</td></tr>
<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org.</td></tr>
</table>

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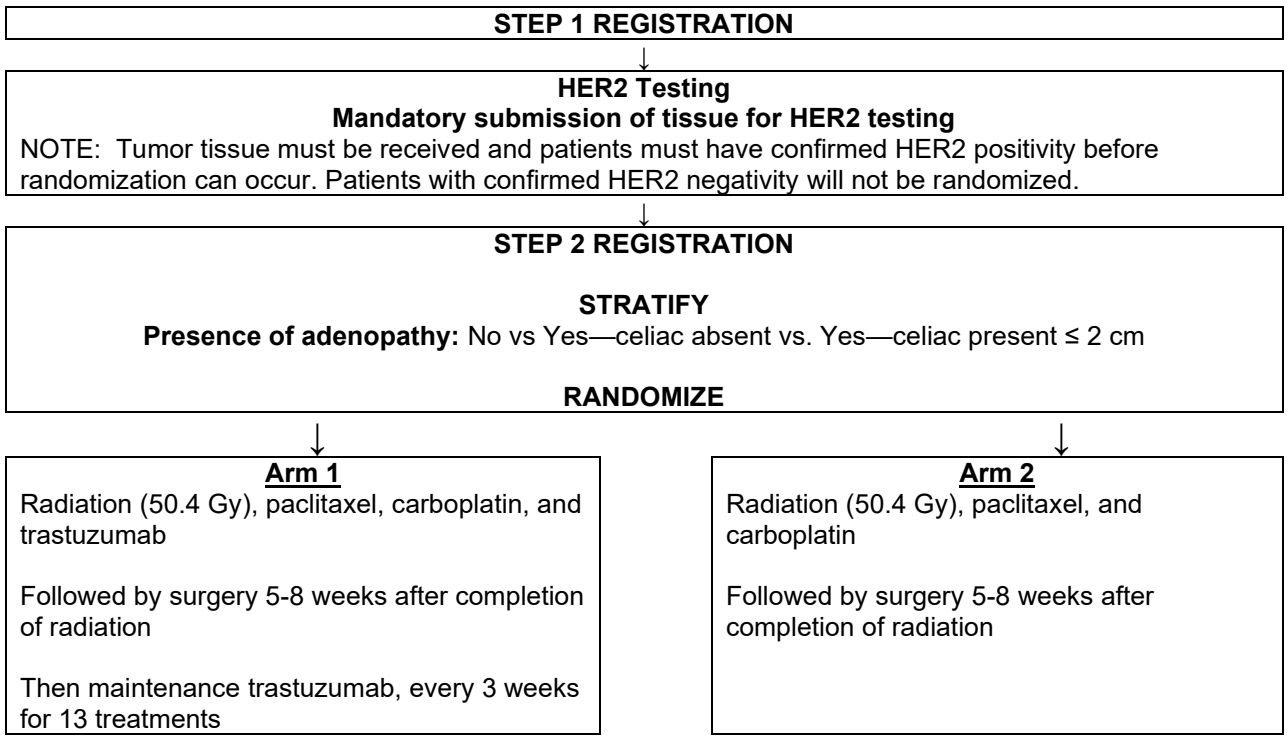
RTOG 1010

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

SCHEMA (2/22/12)



Note: 3D-CRT and IMRT credentialing is required for this protocol; see Section 5.1.

Patient Population: (See Section 3.0 for Eligibility) **(11/5/14)**
Pathologically confirmed HER2 expressing adenocarcinoma of the esophagus, centrally assessed, involving the mid (up to 25 cm), distal and/or esophagogastric junction.

Required Sample Size: 197

ELIGIBILITY CHECKLIST—STEP 1 (12/30/10)
(page 1 of 3)

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_____ (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 $\leq$ 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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_____(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 ≥ 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:

3D-CRT and IMRT 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 (Last First Middle)

_____ 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

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_____ 14. Method of Payment

_____ 15. Any care at VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization Date

_____(Y/N) 18. 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?

_____(Y/N) 19. 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?

_____(Y/N) 20. 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?

_____(Y/N) 21. 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)?

_____(Y/N) 22. 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)?

_____(Y/N) 23. 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)?

_____(Y/N) 24. 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?

_____ (Y/N) 25. Will IMRT be used to treat the patient?

ELIGIBILITY CHECKLIST—STEP 2 (HER2-POSITIVE PATIENTS ONLY) (7/26/11)
(PAGE 1 OF 2)

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Case #

_____ (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. Was the whole-body PET/CT scan performed within the time frame required in Section 3.1?

_____(Y) 5. Was and 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 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: _____

ELIGIBILITY CHECKLIST—STEP 2 (7/16/13)
(page 2 of 2)

NRG Oncology Institution #
RTOG 1010
Case #

_____ 3. Participant Initials (Last, First, Middle)

_____ 4. Verifying Physician

_____ 5. Patient ID

_____ 6. Calendar Base Date

_____ 7. Randomization Date

_____ (Y) 8. Has the Step 2 Eligibility Checklist been completed?

_____ (Y) 9. In the opinion of the investigator, is the patient eligible?

_____ 10. Medical Oncologist's Name

_____ 11. Surgeon Name

_____ (Y/N) 12. Patient has consented to take part in the quality of life study?
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)]

_____ (Y) 14. Is the patient HER2 positive?

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/NRG Oncology 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, $p185^{HER2}$, that is targeted by the humanized anti-$p185^{HER2}$ 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 HER-2/*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 verses 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 benefited 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 0006 (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 regiments (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/m^2, and paclitaxel, 50 mg/m^2, 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)

Adverse Event	Grade 2	Grade 3	Grade 4
Esophagitis	1	1	1
Nausea	4	3	0
Dehydration	1	1	0
Diarrhea	1	0	0
Neutropenia	2	3	1
Allergy	0	0	1
Infection	1	1	0
Cardiac	0	0	0

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.

1.10.1 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.

1.10.2 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=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 NRG Oncology studies, baseline QOL is not mandated as part of the pretreatment evaluation. NRG Oncology 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 NRG Oncology in 21.8% and 24.2% for FACT-E and EQ-5D, respectively. This attrition is demonstrated despite robust efforts on the part of NRG Oncology 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

- 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;
- 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;
- 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;
- To determine if the addition of trastuzumab to trimodality treatment improves the Swallow Index and Eating Index Subscale scores of the FACT-E;
- To determine if the addition of trastuzumab to paclitaxel, carboplatin, and radiation impacts quality-adjusted survival.

3.0 PATIENT SELECTION (11/5/14)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (7/16/13)

3.1.1 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

3.1.2 Endoscopy with biopsy

PRIOR TO STEP 1 REGISTRATION BUT WITHIN 56 DAYS PRIOR TO STEP 2 REGISTRATION

3.1.3. Intent to submit tissue for central HER2 testing per Sections 10.2.2 and 10.2.3

3.1.4 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; PET/CT of skull base to mid-thigh is acceptable) (**NOTE**: if adenopathy is noted on CT or whole-body PET/CT scan, an endoscopic ultrasound is not required prior to STEP 2 registration as long as adequate tissue has been obtained for central HER2 testing, see 3.1.14
- 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

3.1.5 Age ≥ 18

3.1.61 Zubrod performance status 0-2

3.1.7 CBC/differential obtained, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3

- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)

3.1.8 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

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

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

3.1.10 HER2 expressing adenocarcinoma of the esophagus centrally

3.1.11 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

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

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

3.1.14 Stage T1N1-2, T2-3N0-2, according to the AJCC 7th edition staging, based upon the following minimum diagnostic work-up:
- History/physical examination, with documentation of the patient's weight, within 14 days prior to Step 2 registration
- Whole-body PET/CT scan within 56 days prior to Step 2 registration (if only CT performed prior to Step 1 registration)
- Endoscopic ultrasound within 56 days prior to Step 2 registration, unless the patient is found to have adenopathy per CT or whole-body PET/CT scan
- EKG within 56 days prior to Step 2 registration
- Serum creatinine ≤ 2 x the upper limit of normal within 14 days prior to step 2 registration

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

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

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

3.1.18 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:

- Unstable angina in the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- 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 (2/22/12)

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.

4.2 Strongly Recommended Evaluations/Management

4.2.1 Arterial blood gas within 56 days prior to Step 2 registration

5.0 REGISTRATION PROCEDURES (15-NOV-2018)

CTEP Registration Procedures:

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	

Documentation Required	IVR	NPIVR	AP	A
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

Access requirements for OPEN and TRIAD:
Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

See Section 5.2 for information on installing TRIAD for submission of digital RT data *prior to enrolling patients*

5.1 Pre-Registration Requirements for 3D-CRT and IMRT Treatment Approaches

Institutions intending to use IMRT to treat any patients registered to this study must complete the IMRT credentialing requirements. Institutions credentialed for IMRT will automatically be credentialed for the use of 3D-CRT.

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Imaging and Radiation Oncology Core (IROC) Houston web site. Visit http://irochouston.mdanderson.org and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with the IROC Houston must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select “Credentialing”. Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and IROC Philadelphia that the institution has completed this requirement. Subsequently, NRG Oncology Headquarters will notify the institution that the IMRT credentialing requirement has been met. If either gating or target tracking techniques are used for motion management when treating some patients from a particular institution on this protocol, IROC Houston will send a pre-programmed moving table with the lung phantom. This moving table will simulate respiratory motion.

If the institution used abdominal compression or the target motion stay with the stated PTV margins, the institution can use previous credentialing using the IROC Houston head-and-neck phantom in lieu of irradiating the lung phantom.

5.1.2 The institution or investigator must update an existing or complete a new IMRT Facility Questionnaire and a Credentialing Status Inquiry Form (available on the IROC Houston web site, http://irochouston.mdanderson.org) and send it to NRG Oncology for review prior to entering any cases. NRG Oncology will notify the institution when all requirements have been met and the institution is RT credentialed to enter patients onto this study.

5.2 Digital RT Data Submission to NRG Oncology Using TRIAD (11/5/14)

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by the Radiation Therapy Oncology Group (RTOG). TRIAD provides sites participating in RTOG clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. RTOG users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the RTOG web site Core Lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.3 Regulatory Pre-Registration Requirements (15-NOV-2018)

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

IRB Approval:

Each 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 be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the RTOG 1010 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the RTOG link to expand, then select trial protocol #RTOG 1010
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for RTOG 1010 site registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB);
- CTSU IRB/Regulatory Approval Transmittal Sheet(for sites not participating via the NCI CIRB) ;
- CTSU RT Facilities Inventory Form (if applicable)
- IRB/REB approval letter
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to NRG Oncology
- IRB/REB assurance number renewal information, as appropriate

Non-English Speaking Canadian and Non-North American Institutions:
*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.3.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

In addition to the requirements above, Canadian institutions must also 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.

5.4 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)

- 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.

5.5 Registration (11/5/14)

5.5.1 OPEN Registration Instructions

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group roster.
- To perform registrations on protocols for which you are a member of NRG Oncology, you must have an equivalent 'Registrar' role on the NRG Oncology roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the relevant Group roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY (11/5/14)

NOTE: Intensity Modulated RT (IMRT) Is Allowed. Using IMRT requires a phantom irradiation, as described in Section 5.1.1.

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

See Section 5.2 for information on installing TRIAD for submission of digital RT data PRIOR to enrolling patients.

6.1 Dose Specifications (11/5/14)

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 providing the PTV coverage stated in Section 6.1.3 will be 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 (11/5/14)

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 maximum slice thickness of 3-5 mm is required through regions of the gross tumor volume (GTV) and a maximum 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 (2/22/12)

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 para-esophageal 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 set up 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.

6.4.6 IMRT Planning

IMRT plans will optimize the initial treatment of 45 Gy and the boost treatment of 5.4 Gy separately. A simultaneous boost technique is NOT allowed for this protocol. Submitting a composite plan is required.

6.4.7 IMRT Beam Arrangement

A five-field beam arrangement is preferred to minimize the low dose distributed to the lungs. Suggested beam arrangements are:

a. For distal esophagus the following beam arrangement (using IEC coordinate system) is useful for minimizing dose to the heart and lungs: LPO (155), LAO(70-80), AP(0), RAO(280-290), RPO(205). Note that the range of gantry angles for the LAO and RAO fields is due to the fact that one needs to find the best compromise between the amount of heart and lung in the field.
b. For GE-junction esophagus, the following beam arrangement (using the IEC coordinate system) may be substituted if it is better for minimizing dose to the kidney: PA (180º), close to LL (90º+/-10º), LAO (30-35º), RAO (325-330º), close to RL (270º+/-10º). These recommended beam arrangements may be changed to one more fitting for the patient's particular anatomy.

Field verification: As a minimum requirement, institutions are required to obtain verification images at the start of treatment and each week thereafter. Prior to the first treatment images that verify the position of the isocenter placement must be obtained and saved by the institution, but these images will not submitted.

For 3D-CRT this imaging can include individual portal views. Twice weekly imaging can consist of portal views for 3D-CRT and isocenter verification images.

For IMRT orthogonal images verifying isocenter position are required. More frequent (daily) imaging is allowed, particularly for patients treated with motion management techniques, but is not required.

6.5 Critical Structures (7/16/13)

NOTE: All required structures must be labeled per DICOM Standard Name as listed in Section 6.5.3 for submission to TRIAD. Resubmission may be required if labeling of structures does not conform to the list provided.

6.5.1 Organs at risk to be contoured include both lungs, liver, 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 Dose to the organs at risk must meet constraints in the Section 6.7 table.

6.5.3 Standard Structure Names for TRIAD Submission (11/5/14)

Standard Names	Description	Required or not
GTV	Gross Tumor Volume: Includes primary and nodes	**Required**
CTV_4500	Clinical Target Volume for initial fraction group	**Required**
CTV_5040	Clinical Target Volume for boost/cone down fraction group	**Required**
PTV_4500	Planning Target Volume for initial fraction group	**Required**

PTV_5040	Planning Target Volume for boost/cone down fraction group	**Required**
Esophagus	Esophagus	**Optional**
Heart	Heart	**Required**
Liver	Liver	**Required**
Lung_L	Left Lung	**Required**
Lung_R	Right Lung	**Required**
Lungs	Total Lung	**Required**
Kidney_L	Left Kidney	**Required**
Kidney_R	Right Kidney	**Required**
Kidneys	Total Kidneys	**Required**
External	External patient contour	**Required**
SpinalCord	Spinal Cord	**Required**

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 (11/5/14)

Dose constraints must follow the guidelines in the table below. 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.

Structure	Description	Metric	Per Protocol	Variation Acceptable	Variation Unacceptable
Initial Plan					
PTV_4500	PTV 45	Max Dose (Gy, 0.03 cc)	≤ 110% Rx Dose	≤ 113 % Rx Dose	> 113 % Rx Dose
		% PTV receiving 45 Gy	>95%	>90%	<90%
		V50Gy(%)	<10%		>10%
Heart	Heart & Pericardium	Max Dose (Gy, 0.03 cc)	≤ 50Gy	≤ 52 Gy	> 52 Gy
		Mean Dose (Gy)	≤ 30 Gy	≤ 31 Gy	> 31 Gy
		V40	≤ 50%	≤ 55%	> 55%
Boost Plan					
PTV_5040		% PTV receiving 5.4 Gy	>95%	>90%	<90%
		V6Gy(%)	<10%		>10%
Composite Plan					
Lungs	Lungs - PTV	Max Dose (Gy, 0.03 cc)	≤ 110% Rx Dose	≤ 113% Rx Dose	> 113% Rx Dose
		Mean Dose (Gy)	≤ 20 Gy	≤ 21 Gy	> 21 Gy
		V30	≤ 20%	≤ 25%	> 25%
		V20	≤ 25%	≤ 30%	> 30%
		V10	≤ 40%	≤ 50%	> 50%

		V5	≤ 50%	≤ 55%	> 55%
Heart	Heart & Pericardium	Max Dose(Gy, 0.03cc)	≤ 52Gy	≤ 54Gy	> 54Gy
		Mean Dose (Gy)	≤ 32Gy	≤ 34Gy	>34Gy
		V40	≤ 50%	≤ 55%	>55%
Kidneys	Combined Kidneys	Max Dose (Gy, 0.03 cc)	≤ 45 Gy	≤ 50 Gy	> 50 Gy
		V20	≤ 30%	≤ 40%	> 40%
SpinalCord	Spinal Cord	Max Dose (Gy, 0.03 cc)	≤ 45 Gy	≤ 50 Gy	> 50 Gy
Liver	Liver	Mean Dose (Gy)	≤ 21 Gy	≤ 25 Gy	> 25 Gy
		V30	≤ 30%	≤ 40%	> 40%

6.7.1 Elapsed Days/Therapy Interruptions

Elapsed Days

- Per Protocol: 38 – 44 total elapsed days;
- Variation Acceptable: 45-51 total elapsed days;
- Deviation Unacceptable: ≥ 50 total elapsed days

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 ≤ 500; platelet count ≤ 50,000; and > grade 3 radiation-related, non-hematologic toxicity. If the patient develops ≥ grade 3 radiation-related toxicity, radiation therapy and chemotherapy should be withheld. Interruption of therapy may continue until the toxicity has regressed to ≤ 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.

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 deviation unacceptable, but follow up will be continued.

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 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.

6.10 Radiation Adverse Event Reporting

See Section 7.10.

7.0 DRUG THERAPY

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

7.1 Treatment (7/16/13)

Note: Trastuzumab, paclitaxel, carboplatin must be administered within 48 hours (+/- 2 days) of the scheduled date for these therapies.

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

Agent	Dose*	Schedule
Trastuzumab	4 mg/kg IV	Day 1
Trastuzumab	2 mg/kg IV	Day 8, 15, 22, 29, 36
Trastuzumab	6 mg/kg IV	On day 57
Paclitaxel	50 mg/m^2 IV	Day 1, 8, 15, 22, 29, 36
Carboplatin	AUC = 2	Day 1, 8, 15, 22, 29, 36
Radiation	50.4 Gy, at 180 cGy/fx	Day 1-5, 8-12, 15-19, 22-26, 29-33, 36-38

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.

Paclitaxel and carboplatin and trastuzumab may be administered before or after radiation. Paclitaxel, carboplatin and trastuzumab doses do not need to be recalculated for change in body weight as long as the weight change is < 10% of the patients total body weight. However, post-surgery it is recommended that the trastuzumab dose be recalculated based on the body weight at initiation of trastuzumab post-surgery.

7.1.2 Arm 2: Paclitaxel and Carboplatin with Concurrent Radiation

Agent	Dose*	Schedule
Paclitaxel	50 mg/m^2 IV	Day 1, 8, 15, 22, 29, 36
Carboplatin	AUC = 2	Day 1, 8, 15, 22, 29, 36
Radiation	50.4 Gy, at 180 cGy/fx	Day 1-5, 8-12, 15-19, 22-26, 29-33, 36-38

*Based on actual body weight.

Paclitaxel and carboplatin may be administered before or after radiation. Paclitaxel, carboplatin and doses do not need to be recalculated for change in body weight as long as the weight change is < 10% of the patients total body weight.

7.2 Details of Chemotherapy (7/16/13)

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 (+/-2 days). Trastuzumab, 6 mg/kg IV will be given on day 57(+/- 2 days) over 30-90 minutes. 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.

Note: It is recommended that maintenance trastuzumab be administered within 1 day of the scheduled treatment. However, maintenance trastuzumab may be administered +/- 3 days of the scheduled treatment.

7.2.2 Paclitaxel

Paclitaxel 50 mg/m^2 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 (or an equivalent agent per institutional guidelines) 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 (or per institutional guidelines). 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 Trastuzumab (Herceptin®) Study Agent Information [NSC 688097; IND] (8/20/13)

7.3.1 *Investigator Brochure*

To supplement the toxicity information contained in this document, all investigators who receive a copy of the protocol also should obtain the current version of the Investigator's Brochure (IB) for comprehensive pharmacologic and safety information.

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 240-276-6575. Please refer to the Pharmaceutical Management Branch, CTEP, DCTD, NCI "Policy and Guidelines for Investigational Agent Distribution" at the following link: http://www.rtog.org/ResearchAssociates/QualityControlSiteAudits/PMBPolicy.aspx. NRG Oncology applies these policies to all provided drug.

7.3.2 *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.

7.3.3 *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**.

7.3.4 *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.

7.3.5 *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 trastuzumab from NCI's Pharmaceutical Management Branch (PMB). The updated version (11/10/03) of each institution's Drug Authorization Review and Tracking System (DARTS) will require selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the Investigator during the annual Investigator registration process. This process must be completed before a drug order can be entered for that investigator. Any changes to this information will require updating the first two pages of the IDF, having the Investigator sign the revised IDF, and returning it to the PMB via fax at 240-276-7893. Questions about the process should be directed to the PMB at 240-276-6575 Monday through Friday from 8:30 am–4:30 pm 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. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to the OAOP application and the associated training guide is available at the following link: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx .

Access to OAOP requires the establishment of a **CTEP Identity and Access Management (IAM) account** https://eapps-ctep.nci.nih.gov/iam/ and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call 240-276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or e-mail PMBAfterHours@mail.nih.gov anytime.

7.3.6 *Adverse Events* (6/13/16)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Trastuzumab (Herceptin, NSC 688097)

The Comprehensive Adverse Events 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 Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4621 patients.* Below is the CAEPR for trastuzumab (Herceptin).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, April 14, 2016[1]

Adverse Events with Possible Relationship to Trastuzumab (Herceptin) (CTCAE 4.0 Term) [n= 4621]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
	Febrile neutropenia[2]		
CARDIAC DISORDERS			
	Cardiac disorders - Other (cardiomyopathy)		
	Heart failure		
	Left ventricular systolic dysfunction		***Left ventricular systolic dysfunction (Gr 3)***
	Pericardial effusion		
	Pericarditis		
	Sinus tachycardia[3]		***Sinus tachycardia[3] (Gr 2)***
	Supraventricular tachycardia[3]		
EYE DISORDERS			
	Conjunctivitis		
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
	Mucositis oral		***Mucositis oral (Gr 2)***
	Nausea		***Nausea (Gr 3)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[3]		***Chills[3] (Gr 2)***
	Edema limbs		

Adverse Events with Possible Relationship to Trastuzumab (Herceptin) (CTCAE 4.0 Term) [n= 4621]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Fatigue			***Fatigue (Gr 3)***
	Fever[3]		***Fever[3] (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
	Pain		***Pain (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[4]	
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 3)***
INVESTIGATIONS			
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Cardiac troponin I increased		
	Ejection fraction decreased		***Ejection fraction decreased (Gr 3)***
	GGT increased		***GGT increased (Gr 2)***
	Neutrophil count decreased[2]		***Neutrophil count decreased[2] (Gr 4)***
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Bone pain		***Bone pain (Gr 2)***
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		***Tumor pain (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache		***Headache (Gr 2)***
	Peripheral sensory neuropathy		
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Adult respiratory distress syndrome[3, 4]	
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchospasm[3, 4]	
	Cough		***Cough (Gr 2)***
	Dyspnea[3, 4]		***Dyspnea[3,4] (Gr 3)***

Adverse Events with Possible Relationship to Trastuzumab (Herceptin) (CTCAE 4.0 Term) [n= 4621]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypoxia[4]		***Hypoxia[4] (Gr 2)***
		Pneumonitis[4]	
		Pulmonary edema[4]	
		Pulmonary fibrosis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Nail loss		
	Rash acneiform		***Rash acneiform (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria[3]		***Urticaria[3] (Gr 2)***
VASCULAR DISORDERS			
	Hot flashes		
	Hypertension[3]		
	Hypotension[3]		
	Lymphedema		
	Vascular disorders - Other (vasodilation)		

[1]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.

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

[3]Associated with infusion-related reactions or administration-related reactions (ARRs).

[4]Severe hypersensitivity reactions including angioedema and pulmonary adverse events (e.g., hypoxia, dyspnea, pulmonary infiltrates, pleural effusion, intersitial lung disease, wheezing, and acute respiratory distress syndrome) have been reported.

[5]Infection may include any of the 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on trastuzumab (Herceptin) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that trastuzumab (Herceptin) caused the adverse event:

CARDIAC DISORDERS - Asystole; Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (edema); Chest pain - cardiac; Myocardial infarction; Myocarditis; Palpitations; Sinus bradycardia; Ventricular arrhythmia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
EYE DISORDERS - Dry eye; Extraocular muscle paresis
GASTROINTESTINAL DISORDERS - Ascites; Constipation; Dyspepsia; Enterocolitis; Esophagitis; Gastritis; Gastrointestinal disorders - Other (ischemic bowel); Small intestinal perforation; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Injection site reaction; Malaise; Multi-organ failure; Sudden death NOS
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture

INVESTIGATIONS - Alanine aminotransferase increased; Blood bilirubin increased; Creatinine increased; Platelet count decreased; Weight gain; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Flank pain; Generalized muscle weakness; Muscle weakness left-sided; Neck pain
NERVOUS SYSTEM DISORDERS - Amnesia; Depressed level of consciousness; Dizziness; Encephalopathy; Leukoencephalopathy; Paresthesia; Seizure; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion[4]; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Wheezing[4]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Erythema multiforme; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hematoma; Thromboembolic event

Note: Trastuzumab (Herceptin) 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.

7.4 Paclitaxel Study Agent Information (7/16/13)

Refer to the package insert for comprehensive pharmacologic and safety information.

7.4.1 *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 (27^0 C).

7.4.2 *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_5W, 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.

7.4.3 *Administration*

Paclitaxel, at the appropriate dose and dilution, will be given as a 1-hour infusion. The paclitaxel is mixed in D_5W 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.

7.4.4 *Storage*

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

7.4.5 *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

7.4.6 *Supply*

Commercially available.

7.5 Carboplatin Study Agent Information (7/16/13)

Refer to the package insert for comprehensive pharmacologic and safety information.

7.5.1 *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.

7.5.2 *Administration*

Carboplatin can be infused intravenously over 30-60 minutes. 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 7.10) 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/m^2. 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:

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

7.5.3 *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.

7.5.4 *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:

Vial size	Diluent volume
50 mg	5mL
150 mg	15 mL
450 mg	45 mL

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.

7.5.5 *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.

7.5.6 *Supply*

Commercially available.

7.6 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) 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.
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:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: anshers@mail.nih.gov

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.

7.7 Dose Modifications: Trastuzumab

NOTE: The trastuzumab dose will not be modified.

7.7.1 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.

7.7.2 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.

Relationship of LVEF to facility's LLN	Decrease of <10% from baseline	Decrease of 10-15% from baseline	Decrease of ≥16% from baseline
Within normal limits	Continue	Continue	Hold trastuzumab and repeat MUGA/Echo in 4 weeks
1-5% below LLN	Continue trastuzumab and repeat MUGA/Echo in 4 weeks	Hold trastuzumab and repeat MUGA/Echo in 4 weeks	Hold trastuzumab and repeat MUGA/Echo in 4 weeks
≥ 6% below LLN	Continue trastuzumab and repeat MUGA/Echo in 4 weeks	Hold trastuzumab and repeat MUGA/Echo in 4 weeks	Hold trastuzumab and repeat MUGA/Echo in 4 weeks

- 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.

7.8 Dose Modifications: Paclitaxel and Carboplatin (7/26/11)

All dose modifications will reflect the most severe toxicity that is observed, including hematologic and nonhematologic toxicity, skin toxicity, and creatinine toxicity.

Chemotherapy doses that are missed due to treatment related toxicity are not made up.

7.8.1 Hematologic Adverse Events (2/22/12)

The dose of paclitaxel, carboplatin, trastuzumab, and radiation will be modified according to blood counts within 72 hours of the day of treatment as shown in the table below. Dose reductions of paclitaxel and carboplatin are permanent.

Treatment Day Blood Counts			Dosage
ANC		Platelet Count	
≥ 1,000 mcL	AND	> 75,000 mcL	Full dosage paclitaxel, carboplatin, and trastuzumab.
500-999 mcL	OR	50,000-75,000 mcL	Full dose trastuzumab. Hold carboplatin and paclitaxel.

			Recheck CBC weekly. When ANC > 1,000 and Plt > 75,000, resume paclitaxel at 1 dose level reduction and carboplatin at 1 dose level reduction.
< 500 mcL	OR	< 50,000 mcL	Hold XRT, carboplatin, paclitaxel, and trastuzumab; Recheck CBC weekly. When ANC > 500 and Plt > 50,000 resume XRT, full-dose trastuzumab. When ANC >1,000 and Plt > 75,000 resume paclitaxel and carboplatin and reduce both by 1 dose level.

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/m^2.

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.

7.8.2 Nonhematologic Adverse Events

Nonhematologic adverse events that will require dose reductions of paclitaxel or carboplatin include treatment related diarrhea, mucositis, esophagitis, and nausea/vomiting/dehydration despite adequate treatment with antiemetic therapy (including substance p antagonists and 5-HT3 antagonists) and treatment related pulmonary toxicity. Dose reductions of paclitaxel and carboplatin are permanent.

Toxicity	Grade	Agent	Modification
1st Episode Grade 3 or 4 (for the adverse events described in 7.6.2)	≥ grade 3	Carboplatin Paclitaxel Trastuzumab	Hold until ≤ grade 2; resume, dose, reducing carboplatin by 1 dose level and paclitaxel by 1 dose level; no dose reduction for trastuzumab
2nd Episode	≥ grade 3	Carboplatin Paclitaxel Trastuzumab	Hold until ≤ grade 2; resume dose, reducing carboplatin by 1 dose level and paclitaxel by 1 dose level; no dose reduction for trastuzumab
3rd Episode	≥ grade 3	Carboplatin Paclitaxel Trastuzumab	Discontinue all carboplatin, paclitaxel. Resume trastuzumab when ≤ grade 2
Paclitaxel infusion-related reaction	≥ grade 4	Paclitaxel	Discontinue paclitaxel. Trastuzumab, carboplatin, and radiation may be continued.
Carboplatin infusion-related reaction	≥ grade 4	Carboplatin	Discontinue carboplatin. Trastuzumab, paclitaxel, and radiation may be continued.

7.9 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 NRG Oncology. Dr. Safran and Dr. Leichman will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. 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 NRG Oncology, whichever occurs first.

7.10 Adverse Events (15-NOV-2018)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.10.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.10.2 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.11 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.11. Contact the CTEP-AERS Help Desk if assistance is required

Definition of an SAE: Any adverse drug event (experience) occurring at any dose 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

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.10.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.11 CTEP-AERS Expedited Reporting Requirements (4/17/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site,

https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613
.

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to both the NCI at 301-230-0159 and the NRG Oncology dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

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

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND [or Non-CTEP IND]: None
Not applicable

8.0 SURGERY (7/16/13)

- If a stent is placed for nutritional support, it must be placed after EUS. Note: if imaging demonstrates adenopathy, then an EUS is not required.
- All patients are highly recommended 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.
- 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.
- 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).
- 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, Dennis Wigle, MD, PhD, who will perform the review after complete data for 20 cases have been received at NRG Oncology. Dr. Wigle will perform the next review after complete data for the next 20 cases enrolled have been received at NRG Oncology. 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 NRG Oncology, 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 (11/5/14)

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 (7/26/11)

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue, blood, and urine. The

NRG Oncology Biospecimen Bank 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 NRG Oncology Biospecimen Bank 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) (7/16/13)

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 performed. (Note: endoscopic ultrasound is not required for patients who have adenopathy on CT or whole body PET); 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.

It is imperative 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, if performed, should be sent separately as soon as the EUS has been completed. The biopsy material from the EUS will help ensure that there is adequate tissue for HER2 testing and can also be used for translational research.

10.2.2 Required Pathologic Material for HER2 Testing

- Representative H & E stained slides (can be a duplicate cut H&E or the diagnostic H&E slide)
- 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 are an acceptable alternative to block submission.
- A Pathology Report documenting that the submitted block contains tumor; the report must include the NRG Oncology 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) must accompany the tissue that is being submitted for HER2 testing.
- A Specimen Transmittal (ST) form and pathology report must accompany the specimens for all patients who consented to the optional tissue/specimen collection.
- Sites can access the form (no password required) at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1010&mode=html&ptid=383 (under "RTOG 1010"). The form must be filled out **completely** and indicate whether the patient has consented to banking of any leftover tissue. The ST form is the standard form required for the optional tissue/specimen collection and it will be forwarded to the Biospecimen Resource Center after HER2 testing is complete for those patients who consented to tissue banking

- 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.

- *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.

- *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 NRG OncologyRegistration.

  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 NRG Oncology to return submitted tissue blocks to the site.

10.3 Specimen Collection for Banking Recommended (11/5/14)

For patients who have consented to participate in the optional specimen banking component of the study

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, whether there tumor is determined to be HER2 positive or negative , will be given the opportunity to participate in tumor tissue banking. If the patient consents, then any tumor tissue remaining after HER2 determination will be sent from Dr. Resnick's laboratory to the NRG Oncology Biospecimen Bank.
- 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 NRG Oncology Biospecimen Bank for banking; if the institution is not able to release the blocks, then an H&E from the original block and a 2 mm punch of the FFPE block or an H&E with 10 unstained slides are 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 NRG Oncology Biospecimen Bank (see Section 10.3.3).

See Appendix V 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 NRG Oncology Biospecimen Bank:
(1) A Pathology Report documenting that the submitted block contains tumor; the report must include the NRG Oncology 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 tumor, whole blood, plasma, and urine; (3) the NRG Oncology 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 (ST) the storage conditions used and time stored.

10.3.3 Specimen Collection Summary

Mandatory Specimens (All Patients)			
Specimens:	Collected When:	Submitted As:	Shipped:
Corresponding H&E stained slides of the primary tumor	Removed at diagnostic endoscopy	H&E stained slide(can be a duplicate H&E slide or the diagnostic slide)	Dr. Resnick Rhode Island Hospital, Providence
1 block primary tumor OR 12 unstained slides from the primary block	Removed at diagnostic endoscopy	Formalin fixed paraffin-embedded block	Dr. Resnick Rhode Island Hospital, Providence
Mandatory Specimens (All Patients)			
1 block primary tumor OR 12 unstained slides from the primary block	Removed at endoscopic ultrasound (if performed) Biopsy recommended but not required for HER2 + patients	Formalin fixed paraffin-embedded block	Dr. Resnick Rhode Island Hospital, Providence
Corresponding H&E stained slides of the primary tumor	Removed at endoscopic ultrasound (if performed) Biopsy recommended but not required for HER2 + patients	H&E stained slide (can be a duplicate H&E slide or the diagnostic slide)	Dr. Resnick Rhode Island Hospital, Providence

Recommended Specimens (HER2 Positive Patients Only)			
Specimens:	Collected When:	Submitted As:	Shipped:
1 block residual primary tumor or 2-mm punch of block or ten 5 micron unstained slides	Removed at esophagectomy surgery	Formalin fixed paraffin embedded	NRG Oncology Biospecimen Bank, San Francisco Shipped ambient
Corresponding H&E stained slide of the residual primary tumor(matching the block material)	Removed at esophagectomy surgery	H&E stained slide (can be a duplicate H&E slide or the diagnostic slide)	NRG Oncology Biospecimen Bank, San Francisco Shipped ambient
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Before treatment start and after chemoradiation prior to surgery	Frozen plasma samples containing **0.5 mL** per aliquot in 1 mL cryovials (5 to 8)	NRG Oncology Biospecimen Bank, San Francisco Plasma sent frozen on dry ice via overnight carrier (Monday-Wednesday; Canada: Monday-Tuesday) See Appendix V
Whole blood for DNA : 5-10 mL of anticoagulated whole blood in EDTA tube #2(purple/lavender top) and mix	Before treatment start Note: If site missed this collection time point they may collect whole blood for DNA at a later time point instead but must note this on the ST Form.	Frozen whole blood samples containing **1 mL** per aliquot in 1 mL cryovials. (3 to 5)	NRG Oncology Biospecimen Bank, San Francisco Whole blood sent frozen on dry ice via overnight carrier (Monday-Wednesday; Canada: Monday-Tuesday) See Appendix V
10-20 mL clean-catch urine	Before treatment start and after chemoradiation prior to surgery	Two 5-10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20°C or 80°C	NRG Oncology Biospecimen Bank, San Francisco Urine sent frozen on dry ice via overnight courier (Monday-Wednesday; Canada: Monday-Tuesday) See Appendix V

10.3.4 Submit materials for Tissue Banking as follows: **(**7/16/13**)**
Courier Address (Fed Ex, UPS, etc.): For FFPE and Frozen Specimens
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.4 Reimbursement (11/5/14)

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new National Clinical Trials Network (NCTN) Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system.

10.5 Confidentiality/Storage

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.5.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank 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 I.

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.

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/. 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 (15-NOV-2018)

Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1720
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 (7/16/13)

Item	Due
Specimen Form (SP)	**To be submitted with tumor sample for HER2 testing to Dr. Resnick (see Section 10.2.2) after Step 1 registration**
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Quality of Life/Health Utility Forms ▪ FACT-E **(FA)** ▪ EQ-5D **(HP)**	Within 2 wks of Step 2 registration
Treatment Form **(TF)**	Within 1 wk of concurrent systemic treatment completion
Radiotherapy Form **(T1)** Daily Treatment Record **(T5) [copy to HQ**	Within 1 wk of RT end
Post Treatment Response Form **(F2)**	4-6 weeks after the last radiation treatment

	post biopsy
Initial Follow-Up Form **(FS)**	Just prior to resection **(must include all toxicities up to the surgical resection)**
Surgical Form **(S1)** Operative Report **(S2)** Surgical Pathology Report **(S5)**	Within 4 wks post surgical resection
Maintenance Treatment Form **(SF)**	Within 1 wk of completion of cycles 1-5, 6-10 and 11-13
Quality of Life/Health Utility Forms ▪ FACT-E **(FA)**	6 wks post chemo/RT but prior to esophagectomy, 1 yr from start of treatment, and 2 yrs from start of treatment
▪ EQ-5D **(HP)**	1 yr from start of treatment and 2 yrs from start of treatment
Follow-Up Form **(F1)** **PET/CT or CT Scan Report (C3)**	Every 4 mos from the end of surgery x 2 yrs, then annually

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.2) (11/5/14)

NOTE: ALL DIGITAL RT DATA REQUIRED IN DICOM FORMAT VIA TRIAD ALL REQUIRED STRUCTURES MUST BE LABELED PER DICOM STANDARD NAME AS LISTED IN SECTION 6.5.

Item	Due
Preliminary Dosimetry Information	
†Digital Data Transmission Form **(DT)**	Within 1 week of RT start
CT data, critical normal structures, all GTV, CTV, and PTV contours Digital beam geometry for initial and boost beam sets Doses for initial boost and composite sets of concurrent treated beams Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan RTOG 1010 Datasheet located on the NRG Oncology/RTOG website at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study+1010	
Submit via TRIAD with Digital RT Data listed above	
Final Dosimetry Information	Within 1 week of RT end
Radiotherapy Form **(T1)** Daily Treatment Record **(T5) [copy to HQ]**	

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

- Pathologic complete response at surgery
- Overall survival (OS) (failure: death due to any cause)
- Adverse events
- Health-related quality of life (HRQoL) as measured by FACT-E
- Quality adjusted survival
- Molecular correlates of efficacy
- 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 25 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 25 months (monthly hazard of 0.02773)
- Hazard ratio (experimental/control) = 0.60
- Two-sided test at $\alpha = 0.05$
- Statistical power of 90%
- 5 years of accrual with 3 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 lan-DeMets (Lan 1983) beta spending function 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 2 interim analyses, 162 DFS events are required to detect an increase in median DFS from 15 months to 25 months, translating into a hazard ratio (experimental/control) of 0.60. Given the conditions above, a total sample size of 183 HER2 positive patients will be required to be accrued uniformly over 5 years with an additional 3 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 197 patients**. It is projected that a total of 591 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:

Sample Sizes With 2-Sided Alpha = 0.05

Increase in Median DFS to (months)	Hazard Ratio	90% Power		
		Evaluable Sample Size	Total Sample Size	Total To Be Screened
27 – original	0.56	148	160	480
26.5	0.57	156	168	504
26	0.58	164	177	531
25.5	0.59	173	187	561
25 – revised	0.60	183	197	591

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, α=0.05, chi-squared test and the assumption of an 80% participation rate.

Power Calculations for ECS Score

p_0	p_a	n/arm*	Power
0.30	0.55	73	90
0.30	0.60	73	97
0.40	0.65	73	89
0.40	0.70	73	97
0.50	0.75	73	91
0.50	0.80	73	98

*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 (7/26/11)

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

13.5.1 Statistical Methods

- *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.

- *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

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 of 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 NRG Oncology gastrointestinal cancer committee chair, and the study statistician will review the adverse event data and make appropriate recommendations to the NRG Oncology 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.

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. All grade 3+ nonhematologic adverse events, and all grade 3+ adverse events.

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 162. Under the alternative hypothesis that the addition of trastuzumab will increase median DFS from 15 months to 25 months, the projected numbers of events and the nominal significance levels for rejecting the H_0 or the H_1 for each of these two interim analyses are shown in the table below:

Nominal Significance Levels for Interim Analyses

Interim Analysis	Efficacy: Reject H_0 if p (H_0) ≤	Futility: Reject H_1 if p ≥	# Events (Control Arm)
#1	≤ 0.001	0.83	81
#2	≤ 0.001	0.25	122

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 H_0 (efficacy), then

accrual to the trial will be stopped (if applicable), it will be concluded that the DFS with trastuzumab (Arm 1) is significantly higher than without trastuzumab (Arm 2) and the results will be reported. If the computed p-value is greater67 than or equal to the nominal significance level boundary for rejecting the H_1 (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 1) is significantly higher than without trastuzumab (Arm 2). Otherwise, if the p-value falls between the nominal significance levels for rejecting the H_0 and the H_1, 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 NRG Oncology 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.

FACT-E Scoring and Analysis

- The FACT-E will be scored per the FACT-E Scoring Guidelines (Version 4 www.facit.org), with higher scores indicating better QOL.
- 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.
- 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.
- 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.

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

EQ-5D Scoring and Analysis

- The quality-adjusted survival of each treatment will be evaluated and compared using EQ-5D if the primary endpoint supports the primary hypothesis.
- 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.
- 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 25 months, for HER2 positive patients with esophageal adenocarcinoma. This major analysis will occur after at least 162 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. 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 studies RTOG 9405 and RTOG 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

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	2	5	7
Not Hispanic or Latino	53	137	190
Ethnic Category: Total of all subjects	55	142	197
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	14	37	51
Native Hawaiian or other Pacific Islander	0	0	0
White	40	104	144
Racial Category: Total of all subjects	55	142	197

REFERENCES

American Society of Clinical Oncology. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. *J Clin Oncol*. 1996;14:671-679.

Bang Y, Chung H, Sawaki A, et al. HER2-positivity rates in advanced gastric cancer (GC): Results from a large international phase III trial. *J Clin Oncol.* 2008;26 (May 20 suppl). Abstract 4526.

Besalga J, Carbonell X, Castaneda-Soto NJ, et al. Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule *J Clin Oncol.* 2005;23:2162-2171.

Beseth BD, Bedford R, Isacoff WH, et al. Endoscopic ultrasound does not accurately assess pathologic stage of esophageal cancer after neoadjuvant chemoradiotherapy. *Am Surg*. 2000;66:827-831.

Bosset JF, Gignoux M, Triboulet JP, et al: Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med*. 1997;337:161-167.

Brien TP, Odze RD, Sheehan CE, et al. HER-2/neu gene amplification by FISH predicts poor survival in Barrett's esophagus-associated adenocarcinoma. *Human Pathol*. 2000;31:35-39.

Brooks J, Kesler K, Johnson C, et al. Prospective analysis of quality of life after surgical resection for esophageal cancer: preliminary analysis. *J Surg Oncol*. 2002;81:185-194.

Burmeister BH, Smithers BM, Gebski V, et al: Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol*. 2005;6:659-668.

Burris H, Moore M, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15:2403-2413.

Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: development and validation of general measure. *J Clin Oncol*. 1993;11:570-579.

Cella DF. Manual for the Functional Assessment of Cancer Therapy (FACT) Scales version 2, April 1993.

Darling G, Eton DT, Sulmann J, et al. Validation of the functional assessment of cancer therapy esophageal cancer subscale (FACT-E). *Cancer*. 2006;107:854-863.

Donaldson GW, Moinpour CM. Learning to live with missing quality of life data in advanced-stage disease trials. *J Clin Oncol*. 2005;23:1-5.

Fleming T. One-sample multiple testing procedure for phase II clinical trials. *Biometrics*. 1982;38:143-151.

Freidlin B, Korn EL. A comment on futility monitoring. *Controlled Clinical Trials*. 2002;23:355-366.

Gaast AV, Van Hagen P, Hulshof M, et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with respectable esophageal or esophagogastric junction cancer: results from a multicenter randomized phase III study. J Clin Oncol 28:7s, 2010 (suppl; abstr 4004).

Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. *Stat Med*. 1990;9:1256-1276.

Grugan KD, Nakagawa H. HER2 amplification in micrometastatic esophageal cancer cells predicts prognosis. *Cancer Cell*. 2008;13:441-453.

Halyard MY, Pisansky TM, Dueck AC, et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: Tolerability and adverse event data from the NCCTG phase III trial N9831. *J Clin Oncol*. 2009;27:263-2644.

Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med*. 1992;326:1593-1598.

Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology*. 2008;52:797-805.

Ilson DH. Chemoradiotherapy in esophageal cancer: toxicity is in the eye of the beholder. *J Thorac Oncol*. 2009;3:277-278.

Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHER Trial. *J Clin Oncol*. 2009;27:5685-5692.

Joensuu, H, Kellokumpu-Lehtinen, PL, Bono, P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354:809-820.

Jones R, Horbach S, Sander P, et al. Heartburn in patients with gastro-oesophageal reflux disease in Germany and Sweden: a study on patients' burden of disease. P*harmacoeconomics*. 2003;15:1091-1102.

Kachnic LA, Scott C, Wasserman T, et al. One year follow-up reveals no difference in quality of life between high dose and conventional dose radiation: a quality of life assessment of RTOG 94-05. American Society for Therapeutic Radiology and Oncology 43rd Annual Meeting, November 2001; San Francisco, Ca.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Stat Assoc*. 1958;53:457-481.

Kleinberg L, Eapen S, Hamilton S, et al: E1201: An Eastern Cooperative Oncology Group (ECOG) randomized phase II trial to measure response rate and toxicity of preoperative combined modality paclitaxel/cisplatin/RT or irinotecan/cisplatin/RT in adenocarcinoma of the esophagus. *Proc Am Soc Ther Radiat Oncol*. 2006. Abstract 156.

Kleinberg L, Forastiere AA. Chemoradiation in the management of esophageal cancer. *J Clin Oncol*. 2007; 25:4110-4117.

Ku GY, Ilson DH. Role of neoadjuvant therapy for esophageal adenocarcinoma. *Surg Oncol Clin N Am*. 2009; 18:533-546.

Lan KKG, DeMets ER. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70: 659-663.

Mackey, J, McLeod, D, Ragaz, J, et al. Adjuvant targeted therapy in early breast cancer. *Cancer.* 2009; 115:1154-1168.

Makuda H, Toi M, Hirai T, et al. Clinical significance of the expression of epidermal growth factor and its receptor in esophageal cancer. *Cancer.* 1991;68:142-148.

Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep.* 1966;50:163-170.

Mendelsohn J. Epidermal growth factor receptor as a target for therapy with antireceptor monoclonal antibodies. *J Natl Cancer Inst Monogr*. 1992;13:125-131.

Minsky BD, Neuberg D, Kelsen DP, et al: Final report of Intergroup trial 0122 (ECOG PE-289, RTOG 90-12): phase II trial of neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys*. 1999;43:517-523.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549-556.

Ott K, Weber WA, Lordick F, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol*. 2006;24:4692-4698.

Overcash J, Extermann M, Parr J, et al. Validity and reliability of the FACT-G subscale use in older person with cancer. *Am J Clin Oncol*. 2001;24:591-596.

Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol*. 2004;22:322-329.

Perez, EA, Romond, EH, Suman, VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer [abstract]. *J Clin Oncol.* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement): 512.

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659-1672.

Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika*. 1977;64:191-199.

Robert NJ, Eiermann W, Pienkowski T, et al. BCIRG 006: Docetaxel and trastuzumab-based regimens improve DFS and OS over AC-T in node positive and high risk node negative HER2 positive early breast cancer patients: quality of life (QOL) at 36 months follow-up. *J Clin Oncol*. 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement): 19647.

Romand EH, Perez EA, Bryan J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673-1684.

Safran H, Suntharalingam M, Dipetrillo T, et al. Cetuximab with concurrent chemoradiation for esophagogastric cancer: assessment of toxicity. *Int J Radiat Oncol Biol Phys*. 2008 70:391-395.

Safran H, Dipetrillo T, Akerman P, et al. Phase I/II study of trastuzumab, paclitaxel, cisplatin and radiation for locally advanced, HER2 overexpressing, esophageal adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2007;67:405-409.

Safran H, DiPetrillo T, Nadeem A, et al. Trastuzumab, paclitaxel, cisplatin, and radiation for adenocarcinoma of the esophagus: a phase I study. *Cancer Invest*. 2004;22:670-677.

Schulz, MW, Chen, J, Woo, HH, et al. A comparison of techniques for eliciting patient preference in patients with benign prostatic hyperplasia. *J Urol*. 2002;168:155-159.

Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235:177-182.

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N *Engl J Med*. 2001;344: 783-792.

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.

Smith, I, Procter, M, Gelber, RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007; 369:29-36.

Swisher SG, Maish M, Erasmus JJ, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. *Ann Thorac Surg*. 2004;78:1152-1160.

Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol.* 2005;23:7811-7819.

Telli ML, Hunt SA, Carlson RW. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility*. J Clin Oncol***.** 2007;25: 3525-3533.

Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III Trial of Trimodality Therapy With Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared With Surgery Alone for Esophageal Cancer: CALGB 9781*. J Clin Oncol.* 2008;26:1086-1092.

Untch, M, Gelber, RD, Jackisch, C, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. *Ann Oncol*. 2008;19:1090-1096.

Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol*. 2001;19:305-313.

Van Cutsem E, Kang Y, Chung H, et al. Efficacy results from the ToGA trial: a phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *Proc Am Soc Clin Oncol*. 2009;LBA 4509.

Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002;20:719-726.

Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med*. 1996;335:462-467.

Weber WA, Ott K, Becker K, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol*. 2001;19:3058-3065.

Williams J, Russell I, Durai D, et al. What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET) Health Technol Assess 2006;10(40):iii-iv,ix-x,1-195.

Wu AW, Jacobson KD, Frick DL, et al. Validity and responsiveness of the EQ-5D as a measure of health-related quality of life in people enrolled in an AIDS clinical trial. *Qual Life Res*. 2002;11:273-282.

Yarden Y, Sliwkowski M. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol*. 2001;2:127-137.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis*. 1974;27:365-375.

APPENDIX I
STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS

Assessments	Prior to Step 1 registration	Prior to Step 1 registration but must be within 56 days prior to Step 2 registration	Within 56 days prior to Step 2 registration	Within 14 days prior to Step 2 registration
Pathologically confirmed diagnosis	X			
Endoscopy w/ biopsy	X			
Endoscopic ultrasound			Pts not exhibiting adenopathy on CT or whole-body PET/CT	
Determination of HER2 status by central laboratory			X	
History/physical w/ weight				X
Chest/abdominal/pelvic CT or whole-body PET/CT		X	X*	
Bronchoscopy			Pts w/ tumors at the level of the carina or above*	
EKG			X	
Med/Rad Onc Surg. Eval			X	
Echocardiogram or MUGA for LVEF			X	
Performance status		X		X
CBC w/ diff, ANC, platelets, Hgb		X		X
Na, K, BUN, Glucose	Within 14 days prior to Step 1 registration			
Creatinine				X
Bilirubin, AST		X		
Pregnancy test (if applicable)		Urine or serum		Serum
Arterial blood gas			Recommended	
PFTs			X	
Plasma/urine for banking, if patient consents (HER2+ patients only)			Before treatment start	

-continued on next page-

APPENDIX I
STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (continued)

Assessments	Prior to Step 1 registration	Prior to Step 1 registration but must be within 56 days prior to Step 2 registration	Within 56 days prior to Step 2 registration	Within 14 days prior to Step 2 registration
Whole blood for banking, if patient consents (HER2+ patients only)			Before treatment start (or at any other visit during or after treatment)	
Tissue for banking, if patient consents (For **all** patients)		Collected from diagnostic biopsy and from endoscopic ultrasound, if performed , and if biopsy performed		
FACT-E, if patient consents				X
EQ-5D, if patient consents				X

* See Section 3.0 for details and exceptions.

APPENDIX I
STUDY PARAMETER TABLE: DURING TREATMENT ASSESSMENTS (7/16/13)

Assessments	**Every wk during chemo/RT**	**After chemo/RT completion and prior to surgery**	**At 6-8 wks post-treatment but prior to surgery**
Endoscopy w/ biopsy		Highly Recommended	
History/physical w/ weight	X	X	
Chest/abdominal/pelvic CT or whole-body PET/CT		X	
Echocardiogram or MUGA for LVEF		X	
Performance status	X	X	
CBC w/ diff, ANC, platelets, Hgb	X	X	
Na, K, BUN, Glucose	X	X	
Creatinine	X		
Bilirubin, AST	Every 2 wks	X	
Adverse event evaluation	X	X	
Plasma/urine for banking, if patient consents (HER2+ patients only)		X	
Tissue for banking, if patient consents (For **all** patients only)	At time of esophagectomy (if performed)		
FACT-E, if patient consents			X

APPENDIX I
STUDY PARAMETER TABLE: FOLLOW-UP ASSESSMENTS (7/16/13)

Assessments	**Every 4 months after surgery for 2 years, then annually**	**At 1 and 2 years from treatment start**
History/physical w/ weight	Arm 1: Every 6 wks during maintenance trastuzumab Arm 2: Every 4 months for 2 years then annually	
Chest/abdominal/pelvic CT or whole-body PET/CT	X	
Echocardiogram or MUGA for LVEF	Arm 1: At 3, 6, 9 and 12 months from the start of maintenance trastuzumab Arm 2: 6 and 12 months post-surgery	
Performance status	X	
Adverse Event Evaluation	X	
FACT-E, if patient consents		X
EQ-5D, if patient consents		X

APPENDIX II

ZUBROD PERFORMANCE SCALE

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

APPENDIX III

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

ESOPHAGUS and ESOPHAGEAL JUNCTION

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 III (Continued)

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

ESOPHAGUS and ESOPHAGEAL JUNCTION

ANATOMIC STAGE/PROGNOSTIC GROUPS

Squamous Cell Carcinoma					
Stage	**T**	**N**	**M**	**Grade**	**Tumor Location****
0	Tis	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1,X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

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

Adenocarcinoma				
Stage	**T**	**N**	**M**	**Grade**
0	Tis	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

APPENDIX IV

Pathology Assessment of the Surgical Specimen

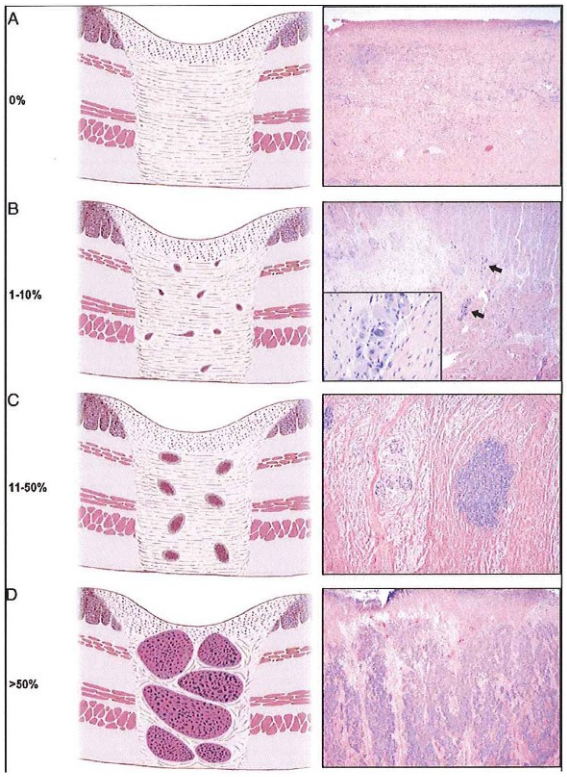
The entire esophageal specimen and lymph nodes will be submitted for local pathological review.

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:

From Wu T, Chirieac LR, Abraham SC, et al. *Am J Surg Pathol*. 2007;31:58-64.



APPENDIX V (11/5/14)

BIOSPECIMEN COLLECTION INSTRUCTIONS

FFPE PLUG KIT INSTRUCTIONS
BLOOD COLLECTION KIT INSTRUCTIONS
URINE COLLECTION KIT INSTRUCTIONS

Shipping Instructions:

US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

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

- ❑ **FFPE Specimens:**
  - o 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.
  - o 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.
  - o 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.

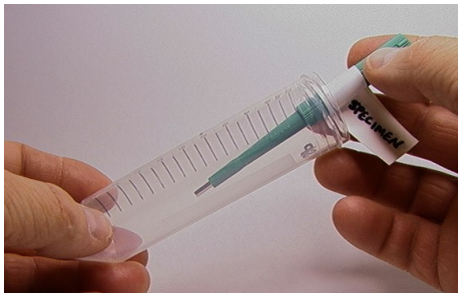
- ❑ **Frozen Specimens**:
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under 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.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o 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 NRG Oncology Biospecimen Bank by email at: RTOG@ucsf.edu or (415)-476-7864 or fax (415)-476-5271**

FFPE SPECIMEN PLUG KIT INSTRUCTIONS

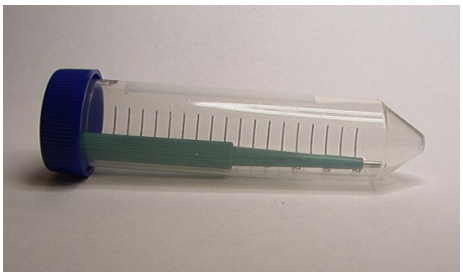
This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

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 NRG Oncology Biospecimen Bank 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 NRG Oncology Biospecimen Bank 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
NRG Oncology Biospecimen Bank at UCSF
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Trackable FFPE shipments
NRG Oncology Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115

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)
- Eighteen (18) 1 ml cryovials
- Specimen Transmittal Form
- Absorbent shipping material (3)
- Biohazard bags (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Kit Instructions
- UN1845 DRY Ice Sticker
- UN3373 Biological Substance Category B Stickers

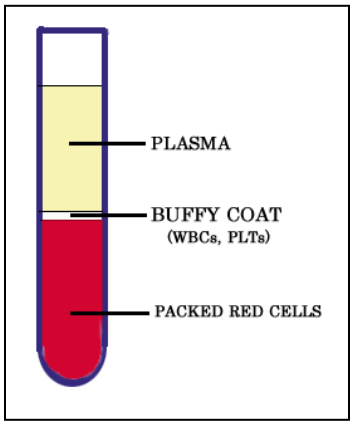
Preparation and Processing of Plasma

A) Plasma: Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 8) as necessary for the plasma collected. Label them with the NRG Oncology 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 ST.
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 (5 to 8) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer. If any aliquots have less than 0.5 ml, the volume must be marked on the aliquot tube.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma -70 to -90° Cuntil 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 ST.

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

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology 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 (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “blood”. If any aliquots have less than 1 ml, the volume must be marked on the aliquot tube.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen -70 to -90° C until ready to ship on dry ice.
5. See below for storage conditions.

BLOOD COLLECTION KIT INSTRUCTIONS (continued)

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

Storage and Shipping:

Freezing and Storage:

- ❑ Freeze Blood samples in a -80C 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.

BLOOD COLLECTION KIT INSTRUCTIONS

- ❑ Include all NRG Oncology paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all, 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)

NRG Oncology Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115Contact Phone 415.476.7864

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 NRG Oncology 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 NRG Oncology 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)**

NRG Oncology Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115

Contact Phone 415.476.7864