

NRG ONCOLOGY
RTOG 1306
A RANDOMIZED PHASE II STUDY OF INDIVIDUALIZED COMBINED MODALITY
THERAPY FOR STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)

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 Research Foundation, Inc.; and SWOG.

Study Team (11JULY2017)

Principal Investigator/

Medical Oncology (Alliance)

Ramaswamy Govindan, MD
Washington University School of Medicine
Box 8056, 660 S. Euclid Avenue
St. Louis, MO 63132
314-362-5737/FAX 314-362-7086
rgovinda@dom.wustl.edu

Medical Oncology Co-Chair (Alliance)

Olwen Hahn, MD
University of Chicago Medical Center
5841 S. Maryland Ave., MC 2115
Chicago, IL 60637
773-702-5381/FAX 773-702-3163
ohahn@medicine.bsd.uchicago.edu

Radiation Oncology Co-Chair (NRG Oncology)

Hak Choy, MD
University of Texas Southwestern
5801 Forest Park Road
Dallas, TX 75390
214-645-7600/FAX 214-645-9193
Hak.Choy@utsouthwestern.edu

Medical Oncology Co-Chair (NRG Oncology/SWOG)

Anne S. Tsao, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 432
Houston, TX 77030
713-792-6363/FAX 792-1220
astsao@mdanderson.org

Radiation Oncology Co-Chair (NRG Oncology)

Billy W. Loo, MD, PhD
Stanford Cancer Institute
875 Blake Wilbur Drive
Stanford, CA 94305
650-736-7143/FAX 650-725-8231
BWLoo@Stanford.edu

Medical Oncology Co-Chair (ECOG-ACRIN)

Nisha A. Mohindra, MD
Northwestern Univ. Feinberg School of Medicine
676 N. St. Clair Street, Suite 850
Chicago, IL 60611
312-695-6180/ FAX 312-695-2351
n-mohindra@northwestern.edu

Radiation Oncology Co-Chair (SWOG)

Megan Daly, MD
University of California Davis
4501 X Street, G-140
Sacramento, CA 95817
916-734-5428/FAX 916-703-5068
megan.daly@ucdmc.ucdavis.edu

Translational Research Co-Chair (Alliance)

Pasi A. Jänne, MD, PhD
Dana-Farber Cancer Institute
450 Brookline Avenue, HIM223
Boston, MA 02215
617-632-6076/FAX 617-632-5786
pjanne@partners.org

Medical Physics Co-Chair (NRG Oncology)

Timothy D. Solberg, PhD, FASTRO, FACR, FAAPM, FACMP
Professor and Vice Chair
UCSF Department of Radiation Oncology
1600 Divisadero Street, Suite H-1031
San Francisco, CA 94115
415-353-7190
Timothy.solberg@ucsf.edu

Pathology Co-Chair (NRG Oncology)

Kirk D. Jones, MD
NRG Oncology Biospecimen Bank
University of California San Francisco
505 Parnassus Ave., Rm M545
San Francisco, CA 94143-0102
415-353-1696/FAX 415-353-1916
kirk.jones@ucsf.edu

NRG ONCOLOGY

RTOG 1306

A RANDOMIZED PHASE II STUDY OF INDIVIDUALIZED COMBINED MODALITY THERAPY FOR STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)

Study Team Continued (11JULY2017)

Senior Statistician (NRG Oncology)
James Dignam, PhD
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19103
215-574-3174/FAX 215-928-0153
dignamj@nrgoncology.org

Senior Statistician (Alliance)
Xiaofei Wang, PhD
Duke University
2424 Erwin Road, Suite 1102
Durham, NC 27705
919-681-5406/FAX 919-681-8028
xiaofei.wang@duke.edu

NRG Oncology Contact Information

Data Manager:

For questions concerning eligibility or data submission

Jeffrey Serianni
NRG Oncology
1818 Market St., Ste. 1720
Philadelphia, PA 19103
215-574-3248/Fax: 215-940-8809
SerianniJ@NRGOncology.org

Amy Krystkiewicz, RN
NRG Oncology
1818 Market St., Ste. 1720
Philadelphia, PA 19103
267-940-9415/Fax: 215-940-8809
KrystkiewiczA@NRGOncology.org

RTQA Questions:

For questions concerning RT data submission

Jennifer Presley, RT(R) (M) (T), ARRT
IROC Philadelphia – RT QA Center
NRG Oncology
1818 Market St., Ste. 1720
Philadelphia, PA 19103
215-574-3153 /Fax:
JPresley@acr.org

RT Credentialing:

<http://irochouston.mdanderson.org>
OR
IROC-Credentialing@mdanderson.org

RT data submission to TRIAD:

Triad-Support@acr.org

Protocol Development:

For questions concerning protocol and informed consent versions & amendments

Fran Bradley
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19013
215-940-8893/Fax: 215-928-0153
BradleyF@NRGOncology.org

NRG ONCOLOGY

RTOG 1306

A RANDOMIZED PHASE II STUDY OF INDIVIDUALIZED COMBINED MODALITY THERAPY FOR STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)

NRG Oncology Contact Information Continued

Lung Committee Chair:

Jeffrey Bradley, MD

Protocol Agent

Agent	Supply	NSC #	IND #
erlotinib	NCI	718781	63383
crizotinib	Commercial/Pfizer		N/A
carboplatin	Commercially available		N/A
cisplatin	Commercially available		N/A
etoposide	Commercially available		N/A
paclitaxel	Commercially available		N/A

Participating Sites (7/29/13)

- U.S. Only
- Canada Only
- U.S. and Canada
- Approved International Member Sites

Document History

	Version/Update Date	Broadcast Date
Amendment 8	July 25, 2017	TBD
Amendment 7	July 11, 2017	TBD
Amendment 6	May 16, 2016	5/31/2016
Amendment 5	September 11, 2015	October 8, 2015
Amendment 4	June 26, 2015	July 13, 2015
Amendment 3	August 27, 2014	September 8, 2014
Update	June 24, 2014	June 24, 2014
Amendment 2	May 29, 2014	June 19, 2014
Activation	September 4, 2013	November 4, 2013
Amendment 1	September 4, 2013	November 4, 2013
Update	July 29, 2013	July 29, 2013
Pre-Activation	March 27, 2013	July 29, 2013

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

This protocol was designed and developed by NRG Oncology. It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by NRG Oncology nor does NRG Oncology assume any responsibility for unauthorized use of this protocol.

NRG ONCOLOGY

RTOG 1306

A RANDOMIZED PHASE II STUDY OF INDIVIDUALIZED COMBINED MODALITY THERAPY FOR STAGE III NON-SMALL CELL LUNG CANCER (NSCLC)

CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (6/26/15)		
To submit site registration documents:	For patient enrollments:	Submit study data
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.cocccg.org (for submitting regulatory documents only)</p>	<p>Please refer to Section 5.0 of the protocol for instructions on using the OPEN system.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions..</p> <p>Do not submit study data or forms to the CTSU Data Operations. Do not copy the CTSU on data submission.</p>
<p>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.</p>		
<p>For clinical questions (i.e. patient eligibility or treatment-related): Contact the Study PI of the Lead Protocol Organization.</p>		
<p>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.</p>		
<p>For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' web site https://www.ctsu.org > education and resources tab > CTSU Operations Information > CTSU Regulatory and Monitoring Policy</p>		
<p>The CTSU web site is located at https://www.ctsu.org</p>		

TABLE OF CONTENTS

SCHEMA	7
ELIGIBILITY CHECKLIST	9
1.0 INTRODUCTION.....	13
1.1 Background	13
1.2 Why This Study Is Important	14
1.3 Previous Studies	15
1.4 Translational Research	16
2.0 OBJECTIVES.....	17
2.1 Primary Objective	17
2.2 Secondary Objectives	17
3.0 PATIENT SELECTION.....	17
3.1 Conditions for Patient Eligibility	17
3.2 Conditions for Patient Ineligibility	18
4.0 PRETREATMENT EVALUATIONS/MANAGEMENT	18
4.1 Highly Recommended Evaluations/Management	18
5.0 REGISTRATION PROCEDURES.....	19
5.1 Phantom Irradiation for IMRT	19
5.2 Digital RT Data Submission Using TRIAD	20
5.3 Regulatory Pre-Registration Requirements	20
5.4 Registration (5/29/14).....	21
6.0 RADIATION THERAPY.....	22
6.1 Dose Specifications.....	22
6.2 Technical Factors/Treatment Planning	22
6.3 Localization, Simulation, and Immobilization	23
6.4 Target Volumes/Motion Management Target Volumes	23
6.5 Critical Structures.....	25
6.6 Documentation Requirements	26
6.7 Compliance Criteria.....	26
6.8 R.T. Quality Assurance Reviews.....	27
6.9 Radiation Therapy Adverse Events	27
6.10 Radiation Therapy Adverse Event Reporting.....	28
7.0 DRUG THERAPY.....	28
7.1 Treatment.....	28
7.2 Erlotinib (Tarceva®, OSI 774), IND #63383.....	30
7.3 Crizotinib (Xalkori®, PF-02341066).....	37
7.4 Cisplatin	42
7.5 Etoposide	42
7.6 Paclitaxel.....	43
7.7 Carboplatin.....	44
7.8 Clinical Trials Agreement	45
7.9 Dose Modification.....	46
7.10 Modality Review	54
7.11 Adverse Events	55
7.12 CTEP-AERS Expedited Reporting Requirements	56
8.0 SURGERY	59
9.0 OTHER THERAPY.....	59
9.1 Permitted Supportive Therapy	59
9.2 Non-permitted Supportive Therapy.....	59
10.0 TISSUE/SPECIMEN SUBMISSION.....	60
10.1 Tissue/Specimen Submission	60
10.2 Tissue Submission for Retrospective Central Review of Biomarker Screening: Mandatory).....	60
10.3 Specimen Collection for Tissue Banking and Translational Research: Highly Recommended (but Optional)	61

10.4	Reimbursement	63
10.5	Confidentiality/Storage	63
11.0	PATIENT ASSESSMENTS	63
11.1	Study Parameters	63
11.2	Details of Evaluations	63
11.3	Measurement of Response	64
11.4	Measurement/Definition of Progression/Recurrence	65
11.5	Criteria for Discontinuation of Protocol Treatment	65
12.0	DATA COLLECTION	65
12.1	Summary of Data Submission	66
12.2	Summary of Dosimetry Digital Data Submission	68
	See Section 5.0 for TRIAD account access and installation instructions	68
13.0	STATISTICAL CONSIDERATIONS	68
13.1	Primary Endpoint	68
13.2	Secondary Endpoints	68
13.3	Sample Size	68
13.4	Patient Accrual	69
13.5	Statistical Design for Translational Research	70
13.6	Analysis Plan	70
13.7	Gender and Minorities	72
	REFERENCES	73
	APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS	76
	APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT	77
	APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP	78
	APPENDIX II: ZUBROD PERFORMANCE SCALE	79
	APPENDIX III: AJCC STAGING SYSTEM	80
	APPENDIX IV: BIOSPECIMEN COLLECTION	82

NRG ONCOLOGY

RTOG 1306

**A Randomized Phase II Study of Individualized Combined Modality Therapy
for Stage III Non-small Cell Lung Cancer (NSCLC)**

SCHEMA (5/29/14)

Institution's Screening for Biomarkers Prior to Randomization: Mandatory

The enrolling institution is responsible for screening (**must be done at CLIA certified lab**) for documentation of EGFR TK mutation and EML4-ALK fusion arrangement.

For EGFR mutation testing, any genotyping method to detect exon 19 deletion, L858, and T790M mutation may be used as long as it is performed in a CLIA certified laboratory. **Note:** The enrolling institution must provide the method of testing and the specific result (i.e. specific mutation).

For ALK testing, the FDA approved Vysis dual color FISH assay must be used for the detection of an ALK rearrangement. **Note:** The enrolling institution must provide the testing laboratory and the specific result (% of positive cells).

Patients with both the EGFR mutation and ALK arrangement will be placed in the ALK Cohort. See [Section 10.0](#) for details of retrospective central review and biomarker analyses.

Weight Loss (in prior 6 mos.)	Stratification Stage	Chemotherapy
1. \leq 5%	1. IIIA	1. cisplatin & etoposide
2. $>$ 5%	2. IIIB	2. paclitaxel & carboplatin

EGFR TK Mutation Cohort

**R
A
N
D
O
M
I
Z
E**

Arm 1: Induction Therapy:

Erlotinib, 150 mg/day for 12 weeks*

Concurrent

†chemotherapy
and IMRT or 3D-CRT
60 Gy in 30 fxs

**Arm 2: Concurrent †chemotherapy and
radiation, 60 Gy**

ALK Tran L Cohort

**R
A
N
D
O
M
I
Z
E**

Arm 3: Induction Therapy:

Crizotinib, 250 mg/bid for 12 weeks*

Concurrent

†chemotherapy
and IMRT or 3D-CRT
60 Gy in 30 fxs

**Arm 4: Concurrent †chemotherapy and
radiation, 60 Gy**

Continued on next page

†Per treating physician's discretion, a choice of 2 chemotherapy regimens:

- Cisplatin and etoposide, every 4 weeks, for 2 cycles;
- Paclitaxel and carboplatin weekly for 6 weeks followed by 2 cycles of consolidation. Consolidation chemotherapy will begin 4-6 weeks after completion of chemoradiation.
- CT scans will be obtained 4-6 weeks after chemoradiation is completed and prior to consolidation chemotherapy administration. See Section 11.2.3 for additional monitoring.

*If CT at 6 weeks into induction therapy does not show at least PR, the patient will proceed directly to concurrent chemotherapy and IMRT or 3D-CRT, provided there is no progression that would preclude definitive chemoradiotherapy, in which case the patient will go off protocol treatment and be treated as appropriate for systemic disease. See Section 11.3 for definitions of responses.

Patient Population: (See [Section 3.0](#) for Eligibility)

Histologically or cytologically confirmed non-squamous NSCLC; unresectable stage IIIA or IIIB disease; patients must be surgically staged to confirm N2 or N3 disease.

Required Sample Size: 156 for the EGFR mutation cohort and 78 for the ALK translocation cohort

ELIGIBILITY CHECKLIST (6/26/15)
(page 1 of 4)

NRG Oncology Institution #
RTOG 1306
Case #

- _____ (Y) 1. Does the patient have a histologically or cytologically confirmed, newly diagnosed non-squamous NSCLC?
- _____ (Y) 2. Does the patient have unresectable clinical stage IIIA or IIIB (AJCC, 7th ed.) disease?
- _____ (Y) 3. Was the patient surgically staged to confirm N2 or N3 disease?
- _____ (Y) 4. Does the patient have measurable disease? (as described in Section 3.1 of the protocol)
- ____ (Y/NA) 5. If the patient has a pleural effusion, does it meet the requirements as outlined in Section 3.1 of the protocol?
- _____ (Y) 6. Did the patient have a pre-enrollment biomarker screening documenting the presence of an EGFR mutation, ALK arrangement, or both (as outlined in Section 3.1 of the protocol)?
- _____ (Y) 7. Did the patient have a complete history and physical within 45 days prior to registration?
- _____ (Y) 8. Did the patient have a whole body FDG-PET/CT, CT scan with contrast of the chest and upper abdomen to include liver and adrenals (unless medically contraindicated), and MRI of the brain with contrast (or CT scan with contrast if MRI medically contraindicated) within 30 days prior to registration?
- _____ (Y) 9. Did the patient have a Zubrod Performance Status of 0 or 1 within 14 days prior to registration?
- _____ (Y) 10. Was the patient at least 18 years old at the time of registration?
- _____ (Y) 11. Did the patient have a CBC/differential within 14 days prior to registration and meet all of the requirements as outlined in Section 3.1 of the protocol?
- _____ (Y) 12. Does the patient have adequate renal and hepatic function within 14 days prior to registration as described in Section 3.1 of the protocol?
- ____ (Y/NA) 13. If the patient is a woman of childbearing potential, has she had a negative serum pregnancy test within 14 days prior to registration?
- _____ (Y) 14. Has the patient provided a signed study specific informed consent prior to study entry including consent for mandatory screening of tissue?
- _____ (N) 15. Does the patient have any component of small cell lung carcinoma?

Continued on next page

ELIGIBILITY CHECKLIST (7/29/13)
(page 2 of 4)

NRG Oncology Institution #
RTOG 1306
Case #

- _____(N) 16. Does the patient have an exudative, bloody, or cytologically malignant effusion?
- _____(N) 17. Has the patient had a prior invasive malignancy (except non-melanomatous skin cancer) and not been disease free for the past 2 years?
- _____(N) 18. Has the patient had prior systemic chemotherapy for the study cancer?
- _____(N) 19. Has the patient had prior radiotherapy to the region of the study cancer that would result in an overlap of radiation therapy fields?
- _____(N) 20. Does the patient have any severe, active co-morbidities as defined in Section 3.2 of the protocol?
- _____(N) 21. Does the patient have atelectasis of the entire lung?
- _____(N) 22. Does the patient have contralateral hilar node involvement?
- _____(N) 23. Has the patient had a prior allergic reaction to the study drug(s) involved in this protocol?

The following questions will be asked at Study Registration:
3D-CRT and/or IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION.

- _____ 1. Institutional person randomizing case.
- _____(Y) 2. Has the Eligibility Checklist been completed?
- _____(Y) 3. In the opinion of the investigator, is the patient eligible?
- _____ 4. Date informed consent signed
- _____ 5. Patient's Initials (Last First Middle)
- _____ 6. Verifying Physician
- _____ 7. Patient ID
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnicity

Continued on next page

ELIGIBILITY CHECKLIST (7/29/13)
(page 3 of 4)

NRG Oncology Institution #
RTOG 1306
Case #

- _____ 11. Gender
- _____ 12. Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Method of Payment
- _____ 15. Any care at a VA or Military Hospital?
- _____ 16. Calendar Base Date
- _____ 17. Randomization date
- _____ 18. Medical oncologist's name
- _____(Y/N) 19. 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) 20. 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) 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 to allow someone from this institution to contact him or her in the future to take part in more research?
- _____(N/Y) 24. Use of IMRT.
- _____ 25. Specify biomarker (EGFR TK mutation, EML4-ALK fusion arrangement, or both).

Continued on next page

ELIGIBILITY CHECKLIST (7/29/13)
(page 4 of 4)

NRG Oncology Institution #
RTOG 1306
Case #

- _____ 26. Specify chemotherapy regimen that patient will receive (cisplatin & etoposide vs. paclitaxel & carboplatin)
- _____ 27. Specify percent weight loss in prior 6 mos. ($\leq 5\%$ vs. $> 5\%$).
- _____ 28. Specify stage (IIIA vs. IIIB).

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 Background

Local-regionally advanced NSCLC is potentially curable with multi-modality therapy. For patients with stage III NSCLC, the standard treatment regimen consists of chemotherapy and radiation. Concurrent administration of platinum based doublet therapy in combination with thoracic radiation is superior to sequential administration of chemotherapy followed by thoracic radiation or thoracic radiation alone (Choy 2004, Blackstock 2007). More than a decade of research with older chemotherapy agents has clearly established that induction chemotherapy preceding concurrent chemoradiation or consolidation or maintenance therapy following chemoradiation does not offer additional improvements in overall survival over concurrent chemoradiation alone (Blackstock 2007). It has become apparent in the recent years that lung cancer, in particular adenocarcinoma, is a remarkably molecularly diverse disease (Wheatley-Price 2008). Although several pathways appear to be dysregulated at a given time, it is widely believed in some cases that cancer cells get addicted to a few pathways more than others (oncogene addiction). Better understanding of the molecular biology of cancer coupled with advances in drug development has led to significant progress recently (Romond 2005; DeMatteo 2009). The spectacular benefit seen with the use of imatinib for the treatment of patients with c-kit harboring Gastrointestinal Stromal Tumors (GIST) and trastuzumab in patients with Her-2 neu positive breast cancer should serve as ideal models for emulation (Romond 2005; DeMatteo 2009). There is a clear need for innovative strategies in the treatment of locally advanced NSCLC and integration of predictive biomarkers for novel targeted agents.

The need for predictive biomarkers is clearly exhibited in the examples below. Despite the significant role played by molecularly targeted therapies, such as bevacizumab and erlotinib, in patients with metastatic NSCLC, results from clinical trials using these agents in the setting of unselected locally advanced NSCLC have not been particularly encouraging (Mok 2009; Shepherd 2005; Cappuzzo 2010; Sandler 2006). More specifically, use of maintenance therapy with gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) following chemoradiation is associated with inferior survival compared to placebo in a molecularly unselected patients with locally advanced NSCLC (Kelly 2008). Concurrent use of EGFR TKIs along with thoracic radiation with or without chemotherapy in patients with locally advanced NSCLC has not produced striking results, once again in a broad unselected group of patients with NSCLC (Ready 2010). Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) in combination with thoracic radiation has resulted in a few instances of tracheo-esophageal fistula leading to early termination of many ongoing trials (Spigel 2010).

The introduction of EGFR TK inhibitors for the treatment of advanced NSCLC and the recognition that the most dramatic responses with EGFR TK inhibitors are best observed in patients whose tumors harbor EGFR TK mutations mark a major milestone in the treatment of patients with NSCLC (Shepherd 2005; Paez 2004). EGFR TK inhibitors administered as monotherapy produce a 2 to 3-fold increase in the response rates, progression-free survival, and overall survival compared to chemotherapy alone in this subset of patients (Fong 2008). When erlotinib, an EGFR TK inhibitor, is administered following 4 cycles of platinum-based doublet therapy in the maintenance setting in patients with incurable advanced NSCLC, there was a significant improvement in the progression-free survival and overall survival of these patients (Hazards Ratio HR 0.10) (Cappuzzo 2010).

It has been reported recently that the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene plays an important role in some patients with NSCLC (Soda 2007). An inhibitor of the ALK fusion kinase, crizotinib, produced a response rate of 64% in 76 patients with advanced metastatic NSCLC who harbored the fusion gene (Kwak 2010). The median progression-free survival has not been reached in this study. The side effects are minimal with the most frequent side effects being visual disturbances, elevated liver function tests, nausea, and vomiting.

Taken together, these examples serve to illustrate the power of a rational drug development process and the impact of targeted therapies in molecularly selected patients. The impressive improvements seen with imatinib in advanced GIST and trastuzumab in metastatic breast cancer led to thoughtful development of these drugs not only in advanced stage disease but also in early stage disease to improve the cure rates. Post-operative trastuzumab improves overall survival by nearly 50% in patients with resected her-2 positive breast cancer. The American College of Surgical Oncology (ACOSOG) reported significant improvement in disease-free survival (primary endpoint) with adjuvant imatinib following resected GIST.

To the best of our knowledge, no studies have been designed specifically targeting patients with an EGFR TK inhibitor with locally advanced NSCLC whose tumors cells have mutated EGFR TK. Given the impressive benefits seen with crizotinib in those with ALK fusion gene, we believe it is rational to study these 2 agents in the molecularly selected patients with locally advanced NSCLC. Tumors that exhibit mutations in the EGFR TK domain do not harbor ALK fusion gene and vice versa. We hypothesize that customized therapy in molecularly selected patients would significantly improve the progression-free survival and overall survival in patients with locally advanced NSCLC when used in addition to chemotherapy and thoracic radiation. Unlike the strategies employed before, we prefer to use targeted therapy (erlotinib or crizotinib) only in the induction phase in a carefully selected group of patients with locally advanced NSCLC whose tumors have known “sensitive” mutations in the EGFR TK domain (for erlotinib) or EML4-ALK fusion rearrangement (for crizotinib). The induction therapy will be followed by concurrent chemoradiation. We do not plan to use molecularly targeted therapy following chemoradiation in light of the discouraging data from SWOG 0023, even though the SWOG 0023 involved the use of gefitinib in a broad group of patients with locally advanced NSCLC without any molecular selection.

1.2 Why This Study Is Important

Even though concurrent chemoradiation improves overall survival in patients with locally advanced NSCLC compared to sequential chemotherapy followed by radiation or thoracic radiation alone, more than 70% would die from recurrent disease. There is a significant need to improve the outcomes in patients with locally advanced NSCLC.

Nearly 10% of all patients with NSCLC diagnosed in the western hemisphere have mutations in the EGFR TK domain. The proportion of patients with EGFR TK mutation increases dramatically to 30%-50% in a group of patients with Asian ethnicity and in those who report no history of tobacco smoking. EGFR TK mutation positive NSCLC perhaps represents the most common molecularly defined subset of NSCLC. EGFR TK inhibitors produce striking response rates (70%-90%) and progression-free survival (12-13 months) in metastatic NSCLC in this subset. Even by conservative estimates, these numbers represent a 2 to 3-fold improvement over chemotherapy alone. Use of EGFR TK inhibitors in a selected group of patients with molecularly vulnerable disease has a high likelihood of improving the outcomes. Moreover, there is extensive experience with regard to the safety and tolerability in advanced disease setting alone, in combination with chemotherapy and in combination with thoracic radiation. ALK fusion gene is present in 3-4% of all patients with NSCLC but probably ~10% in adenocarcinoma of the lung, roughly at the same prevalence rate as EGFR TK mutations. More importantly, the very same group of individuals (adenocarcinoma, light or never smokers) is likely to have one or the other molecular changes we are seeking for this study.

Eligible patients for the proposed study include those with non-squamous NSCLC with EGFR TK mutations or EML4- ALK fusion gene product. Each enrolling institution is responsible for the biomarker screening, which must be done at a CLIA certified laboratory.

If the proposed study meets its primary endpoints, this study itself would likely change the practice patterns. It is highly unlikely that another larger phase III study would be feasible in molecularly defined locally advanced NSCLC. Patients with local-regionally advanced NSCLC will be routinely screened for the presence of EGFR TK mutations (just as patients with breast cancer

are screened for the presence of her-2 overexpression/amplification) and EML4-ALK fusion gene. Individualized therapy would then become the standard of care for patients with stage III NSCLC. Moreover, this study would provide the template for integration of emerging novel therapies for a molecularly defined subset of patients early in the drug development and early in the disease process, significantly enhancing the prospect of cure. It is worth keeping in mind that targeted therapies have not cured a single patient with NSCLC to date. It is critical that we develop rational approaches to cure more patients in early and locally advanced NSCLC with the use of molecularly targeted therapies.

If the proposed study fails to meet its study objectives, cytotoxic chemotherapy will continue to be the standard of care even for patients with locally advanced NSCLC, despite having EGFR TK mutations or ALK fusion gene. Like all well-designed prospective multi-center trials, a negative outcome from this study at least will put to rest the idea that use of targeted therapies will improve survival even in this carefully selected molecularly defined subset. Empiric use of available agents such as EGFR TK inhibitors or ALK inhibitors even in molecularly selected patients could then be strongly discouraged in locally advanced NSCLC.

1.3 Previous Studies

Erlotinib improves overall survival modestly in patients with advanced NSCLC (not based on EGFR mutation status) who have had progressive disease following platinum based chemotherapy (Shepherd 2005). Gefitinib, another EGFR TK inhibitor, has been shown to be non-inferior to docetaxel (an approved agent) in the second line therapy of NSCLC (Kim 2008). Gefitinib produces better progression-free survival over paclitaxel and carboplatin in patients with metastatic previously untreated NSCLC from Asia with no or limited history of tobacco smoking (Mok 2009). Specifically, the improvement is striking and significant only in those with EGFR TK mutation NSCLC. Similar results of striking benefit in EGFR TK mutation NSCLC have been reported from other studies (Cappuzzo 2010).

CALGB 30106 studied the role of induction therapy with gefitinib, paclitaxel, and carboplatin followed by concurrent therapy with thoracic radiation with either gefitinib alone (stratum 1, poor risk group) or gefitinib and weekly paclitaxel, carboplatin (stratum 2, good risk group) (Ready 2010). The median overall survival in the “good- risk” (stratum 2) group was a disappointing 13 months, though surprisingly, was much better in the “poor-risk” group with a median overall survival of 19 months. Of the 45 specimens adequate for EGFR and KRAS mutation analysis, 13 (29%) tumors had EGFR-activating mutations. Two of the tumors with L858R mutations also had T790M mutations that are known to confer resistance to gefitinib. Tumors with an EGFR gefitinib sensitive mutation without a resistance mutation were balanced between the 2 strata with five in poor-risk stratum 1 and six in good-risk stratum 2. The median overall survival was 5.7 months for exon 19 deletions and 28.4 months for exon 21 L858R mutations. These results have to be interpreted with caution given the extremely small numbers and the use of gefitinib in combination with chemotherapy in the “good- risk” group (stratum 2).

Maintenance therapy with gefitinib following concurrent chemoradiation with cisplatin, etoposide, and consolidation docetaxel produced markedly inferior overall survival and a correspondingly decreased progression- free survival compared with placebo in molecularly unselected group of patients with locally advanced NSCLC in the SWOG study (Kelly 2008).

RTOG 94-10 was the largest phase III trial from North America that compared sequential versus concurrent chemoradiation. The RTOG reported the results of this 3-arm trial that included 611 patients. This trial demonstrated the superior outcome of concurrent chemoradiation therapy (Curran 2011). Belani, Choy, and others explored the weekly paclitaxel and carboplatin in locally advanced NSCLC. (Belani 2005, Movsas 2005). The median survival ranges from 16.3 to 17.9 months, which was comparable to other regimens. The toxicity was reasonable.

Physicians will be allowed to choose either of the 2 most commonly used chemotherapeutic regimens in stage III NSCLC: cisplatin and etoposide for 2 cycles concurrent with radiation or

weekly doses of paclitaxel and carboplatin during radiation therapy followed by 2 additional cycles of consolidation therapy with paclitaxel and carboplatin administered every 3 weeks.

1.4 **Translational Research** (6/26/15)

Paired frozen tumor tissue or formalin fixed paraffin embedded tissue and peripheral blood will be obtained from consenting patients in order to obtain genomic DNA. With the limited numbers of samples, it may not be possible to obtain enough high quality material from all the enrolled patients. Therefore, this correlative component should be viewed as an exploratory analysis. DNA will be subjected to custom array capture for targets representing all human tyrosine kinase exons and a subset of associated effector/modulator proteins downstream of EGFR activation pathway and those related to the fusion kinase activity conferred by novel EML4 ALK translocation. Deep (> 200X coverage) re-sequencing will be performed to generate quantitative read counts of both high- and low-frequency somatic mutations among the targeted exons in each patient sample pair. The objective of the correlative study is to assess the feasibility of performing deep sequencing of selected kinomes in patients from whom adequate amount of tissue would be available. Identified genomic alterations (SNVs, InDels, and rearrangements) will be correlated response to therapy.

Lung cancer is molecularly more complex than had been realized previously. Comprehensive sequencing efforts in lung cancer to date have reviewed a diversity of relatively low frequency mutations that may, nonetheless, have biological relevance. Of all the known genetic aberrations, EGFR mutations and ALK rearrangements are clinically highly significant and are targets for therapy. While the presence of these markers (EGFR TK mutation and ALK fusion) predict for response to some extent, more work needs to be done to identify mechanisms of both intrinsic and acquired resistance. Multiple (as yet undiscovered) genomic alterations may collectively contribute to the therapeutic response and survival. Identification secondary alterations in the same or other pathways is now known to contribute to therapeutic resistance to some extent in relation to EGFR TK inhibitors, though much less is known about the genomic evolution in relation to EML4 ALK inhibitors. Finally, because of intrinsic tumor cell heterogeneity and multi-clonality, the “dosage” of a specific mutation, rather than simply its presence or absence in an undefined percentage of the cell population, may drive the magnitude of the therapeutic response and overall clinical outcome.

Accordingly, we hypothesize that “deep” and quantitative re-sequencing of a selected set of genes in lung cancer will better define biomarkers that would more reliably predict response to existing therapies (such as erlotinib and crizotinib) and identify novel targets for future therapy. To test this hypothesis, we will combine array-based target capture and Illumina sequencing of the receptor tyrosine kinome (including EGFR) and the critical genes in the downstream pathways. Sequencing will be performed on patient-matched tumor and non-malignant DNAs for at least 200X coverage to generate quantitative and sensitive data (“deep” read counts) to detect mutations that may occur in subpopulations of tumor cells. Samples will be bar-coded to allow multiplexed resequencing of samples, both to decrease cost and increase throughput of the analysis, with the goal of eventually developing this platform for a prospectively conducted ‘real-time’ assay in subsequent integrated biomarker trials. As compared to more comprehensive whole exome or whole genome studies, this approach will allow us to perform “deeper” (more sensitive) sequencing of at least potentially actionable and thus, more clinically relevant gene targets on a larger number of cases. The relatively lower complexity of sequence data also will allow us to barcode and multiplex samples (lower assay cost) and more rapidly identify and validate true genomic alterations in independent tumor cohorts. Based on the data generated, we will be able to address whether alterations in the tyrosine kinome (in addition to or instead of the specific EGFR analyzed in the primary trial) contribute to therapeutic response and overall outcome.

2.0 OBJECTIVES

2.1 Primary Objective

- 2.1.1 To assess whether patients with unresectable local-regionally advanced NSCLC treated with targeted agents based on molecular characteristics have a longer progression-free survival than those treated with standard care therapy alone

2.2 Secondary Objectives

- 2.2.1 To evaluate response rate;
2.2.2 To assess toxicity;
2.2.3 To assess overall survival;
2.2.4 To correlate clinical outcomes with tumor molecular aberrations identified from deep sequencing of selected kinomes in patients from whom adequate baseline tissue is available.

3.0 PATIENT SELECTION (5/29/14)

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 (6/26/15)

- 3.1.1 Histologically or cytologically confirmed, newly diagnosed non-squamous NSCLC;
3.1.2 Unresectable stage IIIA or IIIB disease; patients must be surgically staged to confirm N2 or N3 disease. Patients may have invasive mediastinal staging by mediastinoscopy, mediastinotomy, EBUS-TBNA, EUS, or VATS.
3.1.3 Patients with any T with N2 or N3 are eligible. Patients with T3, N1-N3 disease are eligible if deemed unresectable. Patients with T4, any N are eligible.
3.1.4 Patients must have measurable disease, i.e., lesions that can be accurately measured in at least 1 dimension (longest dimension in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
3.1.5 Patients with a pleural effusion, which is a transudate, cytologically negative and non-bloody, are eligible if the radiation oncologist feels the tumor can be encompassed within a reasonable field of radiotherapy.
3.1.6 If a pleural effusion can be seen on the chest CT but not on chest x-ray and is too small to tap, the patient will be eligible. Patients who develop a new pleural effusion after thoracotomy or other invasive thoracic procedure will be eligible.
3.1.7 The institution's pre-enrollment biomarker screening at a CLIA certified lab documents presence of known "sensitive" mutations in EGFR TK domain (exon 19 deletion, L858) and/or EML4-ALK fusion arrangement. Either the primary tumor or the metastatic lymph node tissue may be used for testing of mutations.
3.1.8 The institution's pre-enrollment biomarker screening at a CLIA certified lab documents absence of T790M mutation in the EGFR TK domain;
3.1.9 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:
 - History/physical examination, including recording of pulse, BP, weight, and body surface area, within 45 days prior to registration;
 - Whole body FDG-PET/CT (orbits to mid-thighs) within 30 days prior to registration; PET/CT must be negative for distant metastasis.
 - CT scan with contrast of the chest and upper abdomen to include liver and adrenals (unless medically contraindicated) within 30 days prior to registration;
 - MRI of the brain with contrast (or CT scan with contrast, if MRI medically contraindicated) within 30 days prior to registration.
- 3.1.10 Zubrod Performance Status 0-1 within 14 days prior to registration;
3.1.11 Age ≥ 18 ;
3.1.12 CBC/differential obtained within 14 days prior to registration, with adequate bone marrow function defined as follows:
 - Absolute neutrophil count (ANC) $\geq 1,000$ cells/mm³;
 - Platelets $\geq 100,000$ cells/mm³;

- Hemoglobin \geq 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb \geq 8.0 g/dl is acceptable.);
- 3.1.13** Adequate renal and hepatic function, defined as follows:
- Serum creatinine $<$ 1.5 mg/dL or Calculated Creatinine Clearance \geq 50 ml/min (by Cockcroft-Gault formula) within 14 days prior to registration;
 - AST/ALT \leq 2.5 X ULN within 14 days prior to registration;
 - Bilirubin within normal institutional limits within 14 days prior to registration
- 3.1.14** Negative serum pregnancy test within 14 days prior to registration for women of childbearing potential;
- 3.1.15** Patient must provide study specific informed consent prior to study entry, including consent for mandatory screening of tissue.

3.2 Conditions for Patient Ineligibility (5/29/14)

- 3.2.1** Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 730 days [2 years] (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
- 3.2.2** Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;
- 3.2.3** Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
- 3.2.4** Atelectasis of the entire lung;
- 3.2.5** Contralateral hilar node involvement;
- 3.2.6** Exudative, bloody, or cytologically malignant effusions;
- 3.2.7** Severe, active co-morbidity, defined as follows:
- Unstable angina and/or congestive heart failure requiring hospitalization within 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;
 - **Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration; Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;**
 - 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 immuno-compromised patients.
- 3.2.8** Pregnancy 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.
- 3.2.9** Prior allergic reaction to the study drug(s) involved in this protocol.

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 Highly Recommended Evaluations/Management

Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.

- 4.1.1** Comprehensive pulmonary consultation and pulmonary function testing, including spirometry and diffusing capacity of carbon monoxide within 56 days prior to start of treatment;
- 4.1.2** EKG and/or echocardiogram within 56 days prior to start of treatment;
- 4.1.3** Quantitative lung ventilation/perfusion scan +/- CT scan within 56 days prior to start of treatment;

- 4.1.4 Nutritional assessment, including evaluation of the need for prophylactic gastrostomy tube placement (if the patient is $\geq 10\%$ below ideal body weight or is unable to swallow pills) within 56 days prior to start of treatment.

5.0 REGISTRATION PROCEDURES (5/29/14)

Access Requirements for OPEN, Rave, and TRIAD

Site staff will need to be registered with CTEP and have a valid and active CTEP-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 Phantom Irradiation for IMRT (5/29/14)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers. The Imaging and Radiation Oncology Core (IROC) Houston QA Center (formerly the Radiological Physics Center [RPC]) will be the entity to notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org	
RT Credentialing Requirements	Treatment Modality	Key Information
	Photons	
Facility Questionnaire	✓	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status inquiry form	✓	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston web site, http://irochouston.mdanderson.org
Phantom Irradiation	✓	An IMRT phantom study provided by IROC Houston must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site, http://irochouston.mdanderson.org . Note that only the most sophisticated technique needs to be credentialed, e.g., if credentialed for IMRT, 3DCRT may be used.
Credentialing Notification		IROC Houston will notify the institution and NRG Oncology that all desired requirements have been met.

5.2 Digital RT Data Submission Using TRIAD (5/29/14)

TRIAD is the American College of Radiology's (ACR's) image exchange application, and it is used by the NRG Oncology. TRIAD provides sites participating in NRG Oncology 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 NCI National Clinical Trial Network. 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 NRG Oncology/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 (6/24/14)

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

Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU web site: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.) An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' web site. Additional information can be found on the CTEP web site at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov.

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 enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at <https://www.ctsu.org> . For sites under the CIRB initiative, IRB data will automatically load to RSS.

Site registration forms may be downloaded from the RTOG-1306 protocol page located on the CTSU members' web site. 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
- Click on the (state organization type e.g. P2C, CITN, NCTN Groupname) link to expand, then select trial protocol, RTOG-1306
- Click on the Site Registration Documents link

Requirements for RTOG-1306 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form (if applicable)

NOTE: Per NCI policy, all institutions that participate on protocols with a radiation therapy component must participate in the IROC Houston monitoring program. If this form has been previously submitted to CTSU, it does not need to be resubmitted unless updates have occurred at the RT facility.

- IRB/REB approval letter
- IRB/REB approved consent (English version)
- IRB/REB assurance number renewal information, as appropriate
- See the additional pre-registration requirements in Sections [5.1](#) and [5.2](#).

5.3.2 Pre-Registration Requirements for the Initial Shipment of Crizotinib

All pre-registration requirements must be met before registering the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the NRG Oncology/RTOG web site, www.rtog.org, under protocol-specific materials/regulatory resources. Institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. The completed SASF document also may be e-mailed to the CTSU at CTSURegulatory@ctsu.cocccg.org.

5.4 **Registration** (6/26/15)

All patients must consent to screening of tissue for EGFR mutation analysis and ALK fusion arrangement at a CLIA certified laboratory. Only patients with EGFR TK mutation or EML4-ALK fusion arrangement will be enrolled. All patients can be registered after completing the Eligibility Checklist via online registration; see the text below for online registration instructions.

5.4.1 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. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster. See Section 5.0 for obtaining a CTEP-IAM account. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. 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 HIPPA authorization form (if applicable).

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 ctscontact@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 (5/29/14)

See [Section 5.2](#) for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

NOTE: FOR THIS STUDY, EITHER IMRT OR 3D-CRT IS REQUIRED.

The use of IGRT is highly encouraged but not required. No margin reduction will be allowed whether IGRT is used or not, and separate IGRT credentialing will not be required. Institutions must complete the pre-registration credentialing requirements in Sections 5.1 through 5.3 before registering patients on this study.

Protocol treatment must begin on day 1 of cycle 1 of chemotherapy.

6.1 Dose Specifications

6.1.1 The total dose will be 60 Gy in 30 fractions of 2 Gy. Radiation treatment will be administered 5 days per week, 1 fraction per day. It is recommended that radiation treatment begin on a Monday, Tuesday, Wednesday, or Thursday. There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily. Radiation therapy (RT) commences on day 1 of chemotherapy. On days when chemotherapy is given concurrently with RT, chemotherapy should be administered prior to RT.

6.1.2 The treatment plan will be normalized such that 95% of the PTV is covered by the prescription dose. No more than 0.03 cc of the PTV may receive > 120% of the prescription dose (maximum dose constraint). The maximum and minimum doses within the PTV (defined as the minimum dose to the hottest 0.03 cc volume and the maximum dose to the coldest 0.03 cc volume, respectively) will be reported.

6.2 Technical Factors/Treatment Planning (5/29/14)

6.2.1 Beam Energy: 6 - 10 MV will be used.

6.2.2 Beam Shaping: Multi-leaf collimation (MLC) or individually-shaped divergent custom blocks will be used to spare normal tissues outside of the target volume.

6.2.3 3D Conformal Radiation Therapy (3D-CRT) or Intensity-Modulated Radiation Therapy (IMRT): The PTV is to be treated with any combination of coplanar or noncoplanar fields optimized to deliver the specified dose while restricting the dose to the normal tissues. Each field is to be treated daily with no revisions throughout the course of treatment. See [Section 5.2](#) for details of

3D-CRT credentialing. IMRT is allowed as long as the participating institution is credentialed for intra-thoracic IMRT treatments. See [Section 5.1](#) for details of IMRT credentialing.

- 6.2.4 Heterogeneity Corrections:** All radiation doses will be calculated with heterogeneity corrections that take into account the density differences within the irradiated volume (e.g., air, soft tissue, or bone). The acceptable heterogeneity correction dose calculation algorithms can be found on the IROC Houston web site at <http://irochouston.mdanderson.org>. Non-validated dose calculation algorithms (e.g. Clarkson or pencil beam) will not be allowed for this study. Dose calculations should be performed on a non-contrast enhanced CT. Alternatively, if calculations are performed on a contrast-enhanced scan, areas of contrast enhancement adjacent to the target volumes or nearby critical structures should be over-ridden with soft tissue density.

6.3 Localization, Simulation, and Immobilization (6/26/15)

- 6.3.1** Immobilization to assure reproducibility of the setup is necessary. Each patient will be positioned in an immobilization device in the treatment position on a flat table.
- 6.3.2** A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV)(see definitions below). Contiguous CT slices, having no more than 3 mm thickness through the regions harboring gross tumor and grossly enlarged lymph nodes and no more than 10 mm thickness of the remaining regions are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. The GTV, CTV, and PTV and normal organs will be outlined on all appropriate CT slices.
- 6.3.3** A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is encouraged for treatment planning. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.
- 6.3.4** Intravenous (i.v.) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, i.v. contrast should be given during the planning CT. If contrast is used, the densities can be over-ridden or the contrast scan must be registered to a non-contrast scan for planning purposes.
- 6.3.5** The use of four-dimensional radiation treatment planning is highly encouraged. Acceptable methods of accounting for tumor motion include: design of the PTV to cover the excursion of the primary and involved nodal CTV during free breathing (motion inclusive), or the more limited excursion during a voluntary or automatic breath-hold (e.g., Elekta ABC device) or a gating approach (e.g., Varian RPM system)

6.4 Target Volumes/Motion Management Target Volumes (5/29/14)

Note: All required structures must be labeled as listed below in Table 6.5.6 for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the DICOM Standard Name listed.

- 6.4.1** Target Volumes: The definitions of volumes will be in accordance with the 1993 ICRU Report #62.
- **Definition of the GTV:** The primary tumor and clinically positive lymph nodes seen either on the pretreatment or the planning CT (> 1 cm short axis diameter) or pretreatment PET scan (maximum SUV > 3) will constitute the GTV. Pathologically involved nodes not meeting radiographic criteria also should be included in the GTV. The volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged.

For patients on Arms 1 and 3, all initially involved sites as determined on CT and/or PET/CT prior to induction therapy will be targeted. At sites of stable disease or partial response to induction therapy, the residual disease/radiologic abnormality (primary or nodal) or residual nodal tissue will constitute the GTV. At nodal sites of complete response to induction therapy with no residual nodal tissue, there will be no GTV but the CTV will be defined as below.

- **Definition of the CTV:** The CTV is defined to be the GTV plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension. However, the CTV should not cross natural anatomic barriers to tumor extension such as fissures or fascial planes unless these

structures are directly abutted or invaded by the GTV. Elective treatment of the mediastinum and supraclavicular fossae will not be done.

For patients on Arms 1 and 3, at nodal sites of complete response to induction therapy with no residual nodal tissue, the CTV is defined to be the pretreatment GTV plus a 0.5 to 1 cm margin, but edited to remain within the anatomic boundaries of the respective nodal stations as seen on the post-induction treatment planning scan (ie, should not extend into lung parenchyma or mediastinal organs unless originally grossly involved).

- Definition of the PTV: The internal target volume (ITV) is defined to be the CTV plus an internal margin (IM) to account for target/organ motion. The final PTV is defined to be the ITV plus a setup margin (SM) to account for patient positioning uncertainty and machine tolerance. These margins are determined as described below.

6.4.2 Margin Determination Based on Motion Management Approaches

- Free-breathing 3-D CT Planning (i.e. standard CT simulation without 4DCT, fusion of inhalation and exhalation scans, or fluoroscopy): The internal motion (IM margin) will be at least 1 cm in the superior-inferior direction, and 0.5 cm in the axial plane. For institutions not using 4DCT, the use of fluoroscopy to determine the margin for motion in the inferior-superior direction is encouraged.
- Breath-hold or gating 3-D CT Planning: For breath-hold (assisted, such as the Elekta ABC device, or voluntary) or gated CT simulation (such as the Varian RPM device), a single 3-D CT image will be acquired at a pre-determined respiration level. The IM will be 0.5 cm in the superior-inferior direction and 0.3 cm in the axial plane. If this approach is adopted, the institution must use breath-hold or respiratory-gated treatment delivery. Treatment delivery under free-breathing conditions without gating is not acceptable for this approach.
- Abdominal Compression: 3-D CT planning: If abdominal compression is used during CT simulation, the IM will be 0.8 cm in the superior-inferior direction and 0.5 cm in the axial plane.
- 4-D CT planning: 4-D CT may be employed (ideally with the acquisition additionally of 3-D CT images at natural end-inhale and end-exhale). The ITV is the union of the CTV volumes (primary tumor and nodes) contoured on each component 3-D CT data set from the 4-D CT acquisition to form the envelope that encompasses the motion of the CTV for a complete respiratory cycle. The portion of the ITV corresponding to tumors completely surrounded by lung parenchyma may be formed by first contouring the maximum intensity projection (MIP) of the GTV, then applying the GTV to CTV margin expansion as described above in "Definition of the CTV".
- Setup Margin (SM): The SM will be 0.5 cm in all directions. No margin reduction will be allowed, even when using IGRT. The final PTV is constructed by expanding the ITV (CTV + IM) by the SM.

Table 6.4.2: PTV Margin Summary (see above for detailed descriptions)

Motion management	Internal margin (cm)		Setup margin (cm, uniform)	Total PTV margin (cm)	
	Sup-Inf	Axial		Sup-inf	Axial
Free breathing	1	0.5	0.5	1.5	1
Breath hold or gating	0.5	0.3	0.5	1	0.8
Abdominal compression	0.8	0.5	0.5	1.3	1
4D CT	Union of CTVs	Union of CTVs	0.5	Union of CTVs + 0.5 cm	Union of CTVs + 0.5 cm

6.5 Critical Structures (7/29/13)

Note: All required structures must be labeled as listed below in Table 6.5.6 for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the DICOM standard name listed.

Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, 4=brachial plexus, and 5=heart. Critical structures should be contoured according to the lung contouring atlas (available at <http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx>).

6.5.1 Spinal Cord: The spinal cord should be contoured based on the bony limits of the spinal canal from the top of C1 to the bottom of L2. The spinal cord dose limit is the highest priority dose constraint and thus must be met irrespective of other constraints. No more than 0.03 cc of the spinal cord may receive greater than 50.5 Gy total dose (“direct” plus “scatter” dose).

6.5.2 Lungs: The total lung volume is defined as the sum of the volume of both lungs minus the GTV. The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The proportion of total lung volume that receives more than 20 Gy (V20) should not exceed 37%. Additionally, the mean lung dose should not exceed 20 Gy.

If either of these constraints is exceeded, for the 3D-CRT cases, one might increase the weighting of any AP/PA fields and reduce any oblique fields. This can be done as long as the cord dose (above), which takes precedence, is not exceeded. For 3D-CRT or IMRT cases, one can reduce the CTV to the minimum range suggested above especially near the spinal cord.

6.5.3 Esophagus: The esophagus contour should include the mucosal, submucosa, and all muscular layers out to the fatty adventitia, from the bottom of the cricoid cartilage to the gastroesophageal junction. No more than 0.03 cc of the esophagus may receive > 63 Gy. The mean dose to the esophagus should be ≤ 34 Gy. The esophagus should not be circumferentially irradiated with > 60 Gy (i.e., the 60 Gy isodose line should not encompass the entire axial cross-section of the esophagus at any level). The V60 (% volume of esophagus exceeding 60 Gy) should be calculated for each patient.

6.5.4 Brachial Plexus: The ipsilateral brachial plexus should be contoured for upper lobe tumors. No more than 0.03 cc of the brachial plexus may receive > 63 Gy.

6.5.5 Heart: The heart and pericardium should be contoured together from the base to the apex of the heart. The following limits are recommended: V60 to <1/3, V45 to <2/3, and V40 to <100% of the heart.

- 6.5.6** DICOM Standard Names for Required Structures for Digital RT Data Submission (5/29/14)
All required RT structures must be labeled using the DICOM Standard Name shown in the table below and submitted digitally.

Table 6.5.6		
Structure	DICOM Standard Name	
Gross Tumor Volume	GTV	Not required if complete response to induction therapy with no residual nodal tissue for patients on Arms 1 or 3. See Section 6.4.1 for details
Clinical Target Volume	CTV	
Internal Target Volume	ITV	IM = internal margin SM = setup margin
Planning Target Volume	PTV_6000	
Right Lung	Lung_R	
Left Lung	Lung_L	
Spinal Cord	SpinalCord	
Lungs	Lungs	Both Lungs minus GTV
Esophagus	Esophagus	
Brachial Plexus	BrachialPlexus	
Heart	Heart	

6.6 **Documentation Requirements (7/29/13)**

Portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter placement for IMRT must be obtained on the first day of therapy but should not be submitted

- 6.6.1** Weekly verification or orthogonal isocenter images are required to be taken, but not submitted. This verification information also can be gathered with cone-beam CT or other CT devices that are present in the treatment room.

- 6.6.2** Isodose plans and DVHs of GTV, CTVs, PTVs, and critical normal structures for IMRT.

- 6.6.3** The “RTOG 1306 Datasheet” is available in the Forms section of the of the NRG Oncology/RTOG web site, <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1306>.

Sites will record dose-volume values for all required structures on this datasheet. The datasheet must be completed and submitted with the digital RT data via TRIAD for review.

6.7 **Compliance Criteria (6/26/15)**

6.7.1 Variations of Dose Prescription:

- Per Protocol: See [Section 6.1](#).
- Variation Acceptable: Variations of this magnitude are acceptable only when the geometrical arrangement of the target and critical structures is challenging. Minimum and maximum doses are defined using a sampling volume of 0.03 cc as described above in Section 6.1.2.
 - PTV: The prescribed dose can cover less than 95% of the PTV provided it covers at least 90% of the PTV. The minimum dose can fall below 93% of the prescribed dose provided it is at least 90% of the prescription dose, if the areas of underdosing are confined to regions of overlap with critical structures. The maximum dose within the PTV may exceed 120% of the prescribed dose provided it is no more than 125% of the prescription dose, and the areas exceeding 110% of the prescription dose are confined within the GTV and do not overlap with critical structures.
 - Spinal cord: Maximum dose \leq 52 Gy.
 - Lungs: V20 \leq 40%, MLD \leq 22 Gy (after all strategies described in section 6.5.2 have been attempted).

- Esophagus: Maximum dose \leq 66 Gy, mean dose \leq 35 Gy. It is recommended that circumferential irradiation to $>$ 60 Gy for no more than 0.5 cm length (e.g., if the CT slice spacing is 0.3 cm, the 60 Gy isodose line may encompass the cross-section of the esophagus on one slice but not on any adjacent slices.)
- Brachial plexus: Maximum dose \leq 66 Gy.
- **Deviation Unacceptable:** Dose distributions falling in this category are not acceptable, and plan modifications should be attempted to improve results. A Deviation Unacceptable occurs if any of the Variation Acceptable dose limits stated above are exceeded. Additionally, a Deviation Unacceptable is assigned if more than 1 cm³ of tissue outside the PTV receives \geq 110% of the prescribed dose.

Table 6.7.1: Summary of Protocol Constraints and Compliance Criteria
(see Sections 6.1, 6.5, and 6.7.1 for detailed definitions)

Structure	Metric	Per protocol	Variation acceptable	Deviation unacceptable
PTV	V60Gy	\geq 95%	\geq 90%	$<$ 90%
	Min dose (0.03 cc)	\geq 55.8 Gy (93%)	\geq 54 Gy (90%)	$<$ 54 Gy
	Max dose (0.03 cc)	\leq 72 Gy (120%)	\leq 75 Gy (125%)	$>$ 75 Gy
Spinal cord	Max dose (0.03 cc)	\leq 50.5 Gy	\leq 52 Gy	$>$ 52 Gy
Lungs (minus GTV)	V20Gy	\leq 37%	\leq 40%	$>$ 40%
	Mean dose	\leq 20 Gy	\leq 22 Gy	$>$ 22 Gy
Esophagus	Max dose (0.03 cc)	\leq 63 Gy	\leq 66 Gy	$>$ 66 Gy
	Mean dose	\leq 34 Gy	\leq 35 Gy	$>$ 35 Gy
Brachial plexus	Max dose (0.03 cc)	\leq 63 Gy	\leq 66 Gy	$>$ 66 Gy

6.7.2 Missed Treatment Days/Elapsed Days

- **Per Protocol:** Treatment break (other than holidays, weekends) 0-2 days; treatment duration: $<$ 45 days;
- **Variation Acceptable:** Treatment break (other than holidays, weekends) 3-7 days; treatment duration: 45-51 days;
- **Deviation Unacceptable:** Treatment break (other than holidays, weekends) $>$ 7 days; treatment duration: $>$ 51 days.

6.8 R.T. Quality Assurance Reviews (5/29/14)

The NRG Oncology Radiation Oncologist Co-Chairs, Hak Choy, MD, and Billy W. Loo, MD, PhD, will oversee quality assurance RT reviews as complete RT data is received. These case reviews will be ongoing and facilitated by IROC Philadelphia RT. The reviews will be performed remotely or at RTOG Headquarters.

6.9 Radiation Therapy Adverse Events

6.9.1 Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving \geq 20 Gy, usually within the first 6 months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

6.9.2 Esophagitis

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If Grade 4 (CTCAE, v. 4) esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify Drs. Choy or Loo.

Esophagitis Grading System (CTCAE, v. 4)

Grade	Clinical Scenario
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; altered eating/swallowing; oral supplements indicated
3	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated
4	Life-threatening consequences; urgent operative intervention indicated
5	Death

Treatment should be interrupted for grade 4 or greater dysphagia or odynophagia. Acute esophageal toxicity, which typically can occur within two weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are provided in the table below.

Management of Radiation Esophagitis

1) Ketoconazole 200 mg PO q day OR
2) Fluconazole 100 mg PO q day until the completion of radiation
3) Mixture of: 2% viscous lidocaine: 60 cc Mylanta: 30 cc sucralfate (1 gm/cc): 10 cc Take 15-30 cc PO q3-4 hrs. prn. (Contraindications: <i>pts on Dilantin, Cipro, Digoxin</i>)
4) Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation
5) Grade 4 esophagitis: hold RT + chemotherapy until grade 2 or less. We expect a significant portion of patients will experience grade 3 esophagitis.

6.10 Radiation Therapy Adverse Event Reporting

See [Section 7.11](#) and [Section 7.12](#).

7.0 DRUG THERAPY (5/29/14)

Protocol treatment must begin within 2 weeks after registration.

7.1 Treatment

All chemotherapy doses will be calculated based on actual body weight. All standard of care chemotherapy is administered as per respective institutional guidelines. All treating physicians will need to declare their treatment choice before randomization of patients on the trial.

In the cohorts randomized to induction erlotinib or crizotinib, radiographic imaging for re-staging will occur at the 6-week time point of induction therapy. **Note:** Any patients who have had no

response (partial or complete) after 6 weeks of induction targeted agent will immediately proceed to chemoradiation.

7.1.1 Control Arm for Both Cohorts (Arms 2 and 4) (9/4/13)

Patients will be treated with the treating physicians' choice of chemotherapy. The treating physician will choose from one of the 2 regimens detailed below and declare the choice prior to patient randomization. Chemotherapy will be administered concurrently with thoracic radiation beginning on day 1 of cycle 1. Any treatment delays or dose reductions should proceed as per institutional guidelines for good medical practice.

Treatment regimen choices are as follows:

- Cisplatin (50 mg/m²) on days 1, 8, 29, and 36 from start of protocol treatment, and etoposide (50 mg/m²) on days 1-5 and 29-33 from the start of protocol treatment administered intravenously for two 4-week cycles;
- Paclitaxel (50 mg/m²) and carboplatin (AUC-2) on days 1, 8, 15, 22, 29, and 36 from start of protocol treatment, intravenously weekly during thoracic radiation for one 6-week cycle. Two cycles of consolidation treatment will begin 4-6 weeks after completion of radiation therapy with paclitaxel (200 mg/m²) and carboplatin (AUC 6) on days 1 and 22 administered intravenously.

7.1.2 EGFR TK Mutation Cohort (Arm 1) (9/4/13)

Patients will receive 12 weeks (four 3-week cycles) of induction therapy with oral erlotinib (150 mg/day) followed by a combination of chemotherapy with thoracic radiation beginning on day 1 of cycle 1 of chemotherapy. Erlotinib induction therapy will be completed 2 weeks prior to initiation of concurrent chemoradiation. Treating physicians will declare the chemotherapy regimen choice prior to randomization.

Treating physicians can choose from 2 chemotherapy regimens:

- Cisplatin (50 mg/m²) on days 1, 8, 29, and 36 from start of protocol treatment, and etoposide (50 mg/m²) on days 1-5 and 29-33 from start of protocol treatment administered intravenously for two 4-week cycles;
- Paclitaxel (50 mg/m²) and carboplatin (AUC-2) on days 1, 8, 15, 22, 29, and 36 from start of protocol treatment, intravenously weekly during thoracic radiation for one 6-week cycle. Two cycles of consolidation treatment will begin 4-6 weeks after completion of radiation therapy with paclitaxel (200 mg/m²) and carboplatin (AUC 6) on days 1 and 22 administered intravenously.

7.1.3 EML4-ALK Fusion Arrangement Cohort (Arm 3) (9/4/13)

Patients will receive 12 weeks (four 3-week cycles) of induction therapy with oral crizotinib (250 mg twice daily) followed by a combination of chemotherapy with thoracic radiation beginning on day 1 of cycle 1 of chemotherapy. Crizotinib induction therapy will be completed 2 weeks prior to initiation of concurrent chemoradiation. Treating physicians will declare the chemotherapy regimen choice prior to randomization.

Treating physicians can choose from 2 chemotherapy regimens:

- Cisplatin (50 mg/m²) on days 1, 8, 29, and 36 from start of protocol treatment, and etoposide (50 mg/m²) on days 1-5 and 29-33 from start of protocol treatment administered intravenously for two 4-week cycles;
- Paclitaxel (50 mg/m²) and carboplatin (AUC-2) on days 1, 8, 15, 22, 29, and 36 from start of protocol treatment, intravenously weekly during thoracic radiation for one 6-week cycle. Two cycles of consolidation treatment will begin 4-6 weeks after completion of radiation therapy with paclitaxel (200 mg/m²) and carboplatin (AUC 6) on days 1 and 22 administered intravenously.

7.1.4 In the unlikely event of a patient having both EGFR TK mutation and EML4-ALK fusion rearrangement and if they are randomized to experimental therapy, patients will be assigned to receive crizotinib induction therapy followed by chemoradiation.

7.2 **Erlotinib** (Tarceva®, OSI 774), IND #63383 (11JULY2017)

To supplement the toxicity information provided in the protocol, investigators must obtain the current version of the Investigator Brochure for comprehensive pharmacologic and safety information. The Investigator's Brochure may be obtained from NCI's Pharmaceutical Management Branch (PMB); see Section 7.2.9 below.

7.2.1 Erlotinib is an orally active antitumor agent (Tyrosine Kinase inhibitor) developed for the treatment of non-small cell lung cancer (NSCLC), pancreatic cancer, and other solid tumors. OSI Pharmaceuticals, Inc., Genentech, Inc., and F. Hoffmann-La Roche Ltd are co-developing erlotinib globally. In the U.S., erlotinib 150 mg daily is approved for use as maintenance therapy in patients with advanced or recurrent NSCLC who have not progressed after 4 cycles of first-line platinum-based doublet chemotherapy.

7.2.2 How Supplied

Erlotinib tablets are provided by Astellas Pharma and distributed by the Pharmaceutical Management Branch, DCTD/NCI as 25 mg, 100 mg, and 150 mg white film-coated immediate-release tablets packaged in high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets.

The tablets are round and convex without markings. The 25 mg tablets are 1/4 inches (6 mm); the 100 mg tablets are 11/32 inches (9 mm); and the 150 mg tablets are 13/32 inches (10 mm). Erlotinib excipients include lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow No. 6 (25 mg only) for product identification.

In 2017 there will be a transition to Erlotinib tablets with a different finished appearance. The new Erlotinib tablets are manufactured to the same specifications, and are packaged in 60 mL HDPE bottles. The tablets are round, with a biconvex face, straight sides, and white film-coated. Each strength will be plain on one side, with print on the opposite side:

- 25 mg – “T” and “25” in orange print
- 100 mg – “T” and “100” in gray print
- 150 mg – “T” and “150” in maroon print

7.2.3 Route of Administration

Oral

7.2.4 Method of Administration

- Tablets should be taken once daily preferably in the morning with up to 200 mL of water one hour before or two hours after food.
- Administration through G-tube: Dissolve the dose in 100 mL of sterile water, and shake it vigorously to form a uniform suspension. Draw suspension into a syringe and administer through the G-tube port. Repeat the transfer until the entire volume has been administered. Add small volume (40 mL) of sterile water to the container used to dissolve the tablets. Shake the residual suspension, aspirate it into a syringe, and administer. Repeat this last step to ensure the entire dose is administered. The total volume of delivery/rinse is ~180 mL.

7.2.5 Potential Drug Interaction

Erlotinib is highly protein bound (92% to 95% in humans). Erlotinib is metabolized primarily via CYP3A4 and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. Dose Erlotinib cautiously with agents that are highly protein bound or are metabolized by, or are inhibitors or inducers of these enzymes.

Significant interactions with the clearance of other CYP3A4 substrates are unlikely.

CYP Iso-Enzymes Inhibitors/Inducers:

- Potent CYP3A4 or combined CYP3A4/CYP1A2 Inhibitors: Use alternative drug. Alternatively, reduce Erlotinib dose in the event of drug interaction (if permitted by the protocol).

- Potent CYP3A4 inducers: Use alternative drug. If an alternative treatment is contraindicated, consider increasing the Erlotinib dose (see [Section 7.9.2](#)).
- Potent and moderate CYP1A2 inducers: concomitant use with Erlotinib should be avoided.

Food-drug interaction: Avoid grapefruit /grapefruit juice (potent CYP3A4) while taking Erlotinib.

Smoking: Advise smokers to stop smoking while Erlotinib. Smoking induces CYP1A2 enzymes and has been shown to reduce Erlotinib exposure by 50% to 60%.

Anticoagulant: Concomitant NSAIDs, warfarin or warfarin-derivatives may increase bleeding and PT /INR. Dose adjustment may be needed.

Proton Pump Inhibitor: Erlotinib's solubility decreases as the pH increases. Co-administration of omeprazole with Erlotinib will increase the AUC and Cmax by 46% and 61%, respectively.

H2-antagonist: Avoid concomitant use of Erlotinib with gastric acid reducing agents if possible. When ranitidine 300 mg is given with Erlotinib, Erlotinib AUC and Cmax decrease by 33% and 54%, respectively. Increasing the dose of Erlotinib will not compensate the loss of exposure. However, if an H2-antagonist receptor is needed, take Erlotinib at least 2 hours before or 10 hours following the H2-antagonist administration. Dosing such, Erlotinib loss of exposure is minimized to AUC of 15% and Cmax of 17%.

Statins: The combination of erlotinib and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

Gastrointestinal perforation: Concomitant use of anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or patients with prior medical history with peptic ulcers or diverticular disease are at high risk of GI perforation while on erlotinib treatment. Discontinue erlotinib if GI perforation manifests.

7.2.6 Storage

Storage: Store at 25°C (77°F); excursions permitted to 15° – 30°C (59° – 86°F).

7.2.7 Patient Care Implications

If patient vomits after taking the tablets, readminister the dose only if the tablets can actually be seen and counted.

Recommend patients to use sunscreen protection, and wear hat and long sleeve shirts as sunlight can exacerbate skin reactions.

Women of childbearing potential must use effective contraception during treatment and for one month after the last dose of Erlotinib.

7.2.8 Adverse Events (25July2017)

A comprehensive list of AEs possibly related to erlotinib is provided in the CAEPR. Additional information can also be found in the Investigator's Brochure. A few common or serious AEs are described below.

Interstitial lung disease (ILD): Cases of ILD-like events, including fatalities, have been reported uncommonly in patients receiving erlotinib for treatment of non-small cell lung cancer (NSCLC), pancreatic cancer, or other advanced solid tumors. In pivotal study BR 21, in NSCLC, the incidence of serious ILD-like events was 0.8% in each of the placebo and erlotinib arms. In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the erlotinib plus gemcitabine group versus 0.4% in the placebo plus gemcitabine-treated group. The overall incidence in patients treated with erlotinib from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Some examples of reported diagnoses in patients suspected of having ILD-like events include

pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, lung infiltration and alveolitis. These ILD-like events started from a few days to several months after initiating erlotinib therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections. In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment initiated as necessary.

Rash or dermatosis: Rash or dermatosis (grades 1-3) has been reported in many subjects (~50%) during the first several days of treatment, although severity diminishes after 4 weeks of therapy. The use of topical agents (*i.e.*, diphenhydramine, corticosteroids) and oral antibiotics (tetracycline) has been instituted in some patients with variable results. In patients with severe rash, treatment has been discontinued or the study drug dose reduced. The etiology of the rash is still unknown, but may be related to the mechanism of action of erlotinib.

Diarrhea, dehydration, and electrolyte imbalance: Diarrhea has occurred in patients on erlotinib, and moderate or severe diarrhea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to treat the dehydration. There have been rare reports of hypokalemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

Hepatotoxicity with or without hepatic impairment: Hepatic failure and hepatorenal syndrome (including fatal cases) can occur with erlotinib treatment in patients with normal hepatic function; the risk of hepatic toxicity is increased in patients with baseline hepatic impairment. Perform periodic liver testing (transaminases, bilirubin, and alkaline phosphatase) during treatment with erlotinib. Increased frequency of monitoring of liver function is required for patients with pre-existing hepatic impairment or biliary obstruction. Withhold erlotinib in patients without pre-existing hepatic impairment for total bilirubin levels >3 x institutional upper limit of normal (ULN) or transaminases >5 x ULN. Withhold erlotinib in patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline. Discontinue erlotinib in patients whose abnormal liver tests meeting the above criteria do not improve significantly or resolve within three weeks.

Renal insufficiencies: Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia, or concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (*e.g.*, pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Withhold erlotinib in patients developing severe renal impairment until renal toxicity is resolved. Perform periodic monitoring of renal function and serum electrolytes during erlotinib treatment.

Gastrointestinal perforation: Gastrointestinal perforation (including fatal cases) can occur with erlotinib treatment. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease may be at increased risk of perforation. Permanently discontinue erlotinib in patients who develop gastrointestinal perforation.

Bullous and exfoliative skin disorders: Bullous, blistering, and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal, can occur with erlotinib treatment. Discontinue erlotinib treatment if the patient develops severe bullous, blistering or exfoliating conditions.

Myocardial infarction/ischemia: In the pancreatic carcinoma trial, six patients (incidence of 2.1%) in the erlotinib/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, three patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.1%), and one died due to myocardial infarction. The pooled incidence of myocardial infarction/ischemia in the three monotherapy lung cancer studies was 0.2% in the erlotinib arms and 0.4% in the control arms.

Cerebrovascular accident: In the pancreatic carcinoma trial, seven patients in the erlotinib/gemcitabine group developed cerebrovascular accidents (incidence: 2.5%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents. The pooled incidence of cerebrovascular accident in the three monotherapy lung cancer studies was 0.6% in the erlotinib arms and 0.9% in the control arms.

Microangiopathic hemolytic anemia with thrombocytopenia: The pooled incidence of microangiopathic hemolytic anemia with thrombocytopenia in the three monotherapy lung cancer studies was 0% in the erlotinib arms and 0.1% in the control arms. The incidence of microangiopathic hemolytic anemia with thrombocytopenia in the pancreatic cancer study was 1.4% in the erlotinib plus gemcitabine arm and 0% in the control arm.

Ocular disorders: Corneal perforation or ulceration can occur with erlotinib treatment. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment and are known risk factors for corneal ulceration/perforation. Interrupt or discontinue erlotinib therapy if patients present with acute/worsening ocular disorders such as eye pain.

Embryo-fetal toxicity: Based on its mechanism of action, erlotinib can cause fetal harm when administered to a pregnant woman. When given during organogenesis, erlotinib administration resulted in embryo-fetal lethality and abortion in rabbits at doses approximately 3 times the recommended human daily dose of 150 mg. If erlotinib is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 2 weeks after the last dose of erlotinib. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking erlotinib.

Women of childbearing potential must use effective contraception during treatment and for one month after the last dose of Erlotinib.

**Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Erlotinib (Tarceva, NSC 718781)**

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 3622 patients.* Below is the CAEPR for Erlotinib (Tarceva).

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 2.6, June 20, 2017¹

Adverse Events with Possible Relationship to Erlotinib (Tarceva) (CTCAE 4.0 Term) [n= 3622]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Disseminated intravascular coagulation ²	
		Hemolytic uremic syndrome ²	
		Thrombotic thrombocytopenic purpura ²	
CARDIAC DISORDERS			
		Myocardial infarction ²	
EYE DISORDERS			
	Conjunctivitis		<i>Conjunctivitis (Gr 2)</i>
	Dry eye		<i>Dry eye (Gr 2)</i>
		Eye disorders - Other (corneal perforation)	
	Eye disorders - Other (eyelash in-growth and/or thickening)		
		Keratitis	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<i>Abdominal pain (Gr 3)</i>
Diarrhea			<i>Diarrhea (Gr 3)</i>
	Dry mouth		<i>Dry mouth (Gr 2)</i>
	Dyspepsia		<i>Dyspepsia (Gr 2)</i>
	Gastrointestinal hemorrhage ³		
		Gastrointestinal perforation ⁴	
	Mucositis oral		<i>Mucositis oral (Gr 3)</i>
	Nausea		<i>Nausea (Gr 3)</i>
Vomiting			<i>Vomiting (Gr 3)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			<i>Fatigue (Gr 3)</i>
HEPATOBIILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection ⁵		<i>Infection⁵ (Gr 3)</i>
INVESTIGATIONS			

Adverse Events with Possible Relationship to Erlotinib (Tarceva) (CTCAE 4.0 Term) [n= 3622]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Alanine aminotransferase increased		Alanine aminotransferase increased (Gr 3)
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		Aspartate aminotransferase increased (Gr 3)
	Blood bilirubin increased		Blood bilirubin increased (Gr 3)
		INR increased (in patients taking Coumadin)	
METABOLISM AND NUTRITION DISORDERS			
Anorexia			Anorexia (Gr 3)
	Dehydration		Dehydration (Gr 3)
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		Dysgeusia (Gr 2)
	Headache		Headache (Gr 2)
		Intracranial hemorrhage	
		Ischemia cerebrovascular ²	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		Cough (Gr 2)
	Dyspnea		Dyspnea (Gr 3)
	Epistaxis		
	Pneumonitis		Pneumonitis (Gr 4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		Alopecia (Gr 2)
	Dry skin		Dry skin (Gr 2)
		Erythema multiforme	
	Nail loss		Nail loss (Gr 2)
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		Pruritus (Gr 2)
	Rash acneiform		Rash acneiform (Gr 2)
Rash maculo-papular			Rash maculo-papular (Gr 3)
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

¹This 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.

²The risk of myocardial infarction, cerebrovascular accident, and microangiopathic hemolytic anemia is increased in patients with pancreatic cancer who were treated concomitantly with gemcitabine.

³Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage,

Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

⁴Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

⁵Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

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

EYE DISORDERS - Blurred vision; Eye disorders - Other (orbital cellulitis); Uveitis; Watering eyes

GASTROINTESTINAL DISORDERS - Colitis; Constipation; Duodenal ulcer; Dysphagia; Esophagitis; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (pneumatosis intestinalis); Pancreatitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs

HEPATOBIILIARY DISORDERS - Cholecystitis

INVESTIGATIONS - Creatinine increased; Lymphocyte count decreased; Platelet count decreased

METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness

NERVOUS SYSTEM DISORDERS - Dizziness; Peripheral sensory neuropathy

PSYCHIATRIC DISORDERS - Confusion

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pharyngolaryngeal pain

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Urticaria

VASCULAR DISORDERS - Thromboembolic event

Note: Erlotinib (Tarceva) 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.

Note: Erlotinib (Tarceva®)-induced diarrhea and/or vomiting has been associated with dehydration, hyperkalemia; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia, increased creatinine, and renal failure.

Note: Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of erlotinib (Tarceva®) in patients with or without baseline hepatic impairment.

7.2.9 Supply:

This study will be conducted under an IND to be held by NCI and will require FDA submission and approval as part of the IND. Erlotinib tablets are provided by Astellas Pharma and distributed by the DCTD/NCI. Erlotinib will be supplied to patients on study free of charge.

7.2.10 This study will be conducted under an NCI IND. The Erlotinib and the associated Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB).

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 erlotinib 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.

The Investigator Brochure (IB), if available, for this drug will be supplied by the PMB/NCI. All requests for IBs should be e-mailed to ibcoordinator@mail.nih.gov <<mailto:ibcoordinator@mail.nih.gov>> or the IB Coordinator may be contacted at 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.

Agent Inventory Records: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Oral Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

7.3 Crizotinib (Xalkori®, PF-02341066) (8/27/14)

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

7.3.1 Crizotinib is a selective ATP-competitive small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) and c-Met/hepatocyte growth factor receptor (HGFR) receptor tyrosine kinases and their oncogenic variants (eg, c-Met/HGFR mutations or ALK fusion proteins). It is manufactured by Pfizer and is FDA approved for use in EML 4 ALK translocated patients with NSCLC.

7.3.2 Formulation

Formulated Capsules: Crizotinib is formulated as a 200 mg or 250 mg capsule. The product consists of crizotinib and compendial excipients in a hard gelatin capsule. Crizotinib is packaged in 60-ct bottles.

7.3.3 Administration

Oral, 250 mg twice daily; Sites will follow standard practice as detailed in the package insert for use with caution in the setting of concomitant drugs.

7.3.4 Storage and Stability

Crizotinib as hard gelatin capsules is supplied in high-density polyethylene (HDPE) bottles. Crizotinib should be stored in accordance with labeled conditions.

7.3.5 Adverse Events (25July2017)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Crizotinib (PF-02341066, NSC 749005)

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 2058 patients.* Below is the CAEPR for Crizotinib (PF-02341066).

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 2.2, April 21, 2017¹

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 4.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<i>Anemia (Gr 2)</i>
CARDIAC DISORDERS			
		Heart failure	
	Sinus bradycardia		
EYE DISORDERS			
Eye disorders - Other (vision disorders) ²			<i>Eye disorders - Other (vision disorders)² (Gr 2)</i>
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<i>Abdominal pain (Gr 2)</i>
Constipation			<i>Constipation (Gr 2)</i>
Diarrhea			<i>Diarrhea (Gr 2)</i>
	Dyspepsia		
		Esophagitis	
	Mucositis oral		
Nausea			<i>Nausea (Gr 2)</i>
Vomiting			<i>Vomiting (Gr 2)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema face			<i>Edema face (Gr 2)</i>
Edema limbs			<i>Edema limbs (Gr 2)</i>
Fatigue			<i>Fatigue (Gr 2)</i>
General disorders and administration site conditions - Other (generalized edema)			
Localized edema			<i>Localized edema (Gr 2)</i>
HEPATOBIILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Alanine aminotransferase increased		<i>Alanine aminotransferase increased (Gr 2)</i>

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 4.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		Aspartate aminotransferase increased (Gr 2)
		Blood bilirubin increased	
	Creatinine increased		
		Electrocardiogram QT corrected interval prolonged	
	Lymphocyte count decreased		
Neutrophil count decreased			Neutrophil count decreased (Gr 2)
	White blood cell decreased		White blood cell decreased (Gr 2)
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		Anorexia (Gr 2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
NERVOUS SYSTEM DISORDERS			
	Dizziness		Dizziness (Gr 2)
	Dysgeusia		Dysgeusia (Gr 2)
	Headache		
	Nervous system disorders - Other (neuropathy) ³		Nervous system disorders - Other (neuropathy)³ (Gr 2)
		Syncope	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Periorbital edema			Periorbital edema (Gr 2)
	Rash ⁴		

¹This 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.

²Vision disorders may include the following: Chromatopsia, Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Vitreous floaters, and Visual perseveration.

³Neuropathy may include the following: Acute polyneuropathy, Amyotrophy, Areflexia, Autoimmune neuropathy, Autonomic failure syndrome, Autonomic neuropathy, Axonal neuropathy, Biopsy peripheral nerve abnormal, Burning feet syndrome, Burning sensation, Decreased vibratory sense, Demyelinating polyneuropathy, Dysesthesia, Electromyogram abnormal, Formication, Gait disturbance, Genital hypoesthesia, Guillain-Barre syndrome, Hyperesthesia, Hypoesthesia, Hyporeflexia, Hypotonia, Ischemic neuropathy, Loss of proprioception, Miller Fisher syndrome, Mononeuritis, Mononeuropathy, Mononeuropathy multiplex, Motor dysfunction, Multifocal motor neuropathy, Muscle atrophy, Muscular weakness, Myelopathy, Nerve conduction studies abnormal, Nerve degeneration, Neuralgia, Neuritis, Neuromuscular toxicity, Neuromyopathy, Neuropathy peripheral, Neuropathy vitamin B6 deficiency,

Neurotoxicity, Paresthesia, Peripheral motor neuropathy, Peripheral nerve lesion, Peripheral nerve palsy, Peripheral nervous system function test abnormal, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal muscular atrophy, Peroneal nerve palsy, Phrenic nerve paralysis, Polyneuropathy, Polyneuropathy chronic, Polyneuropathy idiopathic progressive, Radiation neuropathy, Sensorimotor disorder, Sensory disturbance, Sensory loss, Skin burning sensation, Temperature perception test decreased, Tinel's sign, Toxic neuropathy, and Ulnar neuritis.

⁴Treatment-related rash may include erythematous rash, rash maculo-papular, and pruritus.

Adverse events reported on crizotinib (PF-02341066) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that crizotinib (PF-02341066) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (basophilia); Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Myocarditis; Pericardial effusion; Supraventricular tachycardia

EYE DISORDERS - Blurred vision; Cataract; Optic nerve disorder; Papilledema

GASTROINTESTINAL DISORDERS - Colitis; Colonic perforation; Dysphagia; Esophageal ulcer; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal amyloidosis); Ileus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; General disorders and administration site conditions - Other (failure to thrive); Malaise; Non-cardiac chest pain

HEPATOBIILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatitis); Hepatobiliary disorders - Other (hepatotoxicity)

IMMUNE SYSTEM DISORDERS - Autoimmune disorder

INFECTIONS AND INFESTATIONS - Abdominal infection; Infections and infestations - Other (peridiverticular abscess); Kidney infection; Lung infection; Sepsis; Skin infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Spinal fracture; Wound complication

INVESTIGATIONS - CPK increased; GGT increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (blood testosterone decreased); Investigations - Other (eosinophil count increased); Investigations - Other (monocyte count increased); Investigations - Other (platelet count increased); Platelet count decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (myopathy); Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (hemorrhage, intratumoral); Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Ischemia cerebrovascular; Pyramidal tract syndrome; Seizure; Stroke

PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS - Fetal death

PSYCHIATRIC DISORDERS - Confusion; Delirium; Euphoria

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Renal and urinary disorders - Other (renal cyst); Renal calculi; Urinary retention

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Dyspnea; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress); Respiratory, thoracic and mediastinal disorders - Other (traumatic lung injury)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (drug eruption)

VASCULAR DISORDERS - Hematoma; Hypotension; Phlebitis; Thromboembolic event; Vasculitis

Note: Crizotinib (PF-02341066) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3.6 Supply:

Pfizer will supply crizotinib free of charge to patients on study in the U.S. Crizotinib is an approved, marketed drug that is considered investigational in the context of this clinical trial; however, this clinical investigation of crizotinib meets the criteria for IND exemption as described under title 21 CFR312.2 (b).

7.3.7 Drug Ordering and Accountability

Crizotinib will be distributed by Biologics, Inc. Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

The Study Agent Shipment Form (SASF); available on the NRG Oncology/RTOG web site, www.rtog.org under protocol-specific materials/regulatory resources for U.S. sites must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. The completed SASF document may also be e-mailed to the CTSU at CTSURegulatory@ctsu.cocccg.org.

The drug supply will not be shipped by Biologics, Inc. until the patient has been registered. NRG Oncology will notify Biologics, Inc. to initiate each of these shipments after registration of the patient. Biologics, Inc. will ship a supply of crizotinib sufficient for the entire treatment for patients randomized to Arm 3. Each shipment will include three 60-ct bottles of crizotinib 250 mg capsules. If the patient dose reduces, contact Biologics for a supply of 200 mg capsules. Biologics, Inc. will ship drug according to the following schedule:

RTOG 1306 Shipment Schedule				
Patient Randomized	Initial e-order sent by RTOG	Initial e-order received by Biologics, Inc. (before 2 p.m. EST)	Initial order shipped by Biologics, Inc.	Initial order received at site
Monday	Monday	Monday	Monday	Tuesday
Tuesday	Tuesday	Tuesday	Tuesday	Wednesday
Wednesday	Wednesday	Wednesday	Wednesday	Thursday
Thursday	Thursday	Thursday	Thursday	Friday
Friday	Friday	Friday	Monday	Tuesday

Biologics, Inc. will ship the order “same day” for all orders received before 2 p.m. EST, Monday through Thursday via FedEx Priority Overnight. Orders received after 2 p.m. EST, Monday through Thursday will be processed and shipped the next business morning.

Drug deliveries are restricted during weekends and holidays. Biologics, Inc. observes the following holidays: New Year’s Day, Memorial Day, July 4th, Labor Day, Thanksgiving Day, the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

Upon notification of a new patient enrollment, Biologics, Inc. will place an outbound call to the site contact to confirm that the site’s shipment is being processed. Biologics’ distribution team will monitor packages throughout the duration of transit via the FedEx web site and FedEx One Call Solution (live support). Real-time monitoring enables Biologics to mitigate potential delivery delays.

Please contact the drug distributor listed in the protocol directly for shipment tracking information and anticipated delivery dates or if a shipment has not been received by the expected date.

At the completion of the study, unused supplies will be destroyed at the site according to the institution's policy for drug destruction. Sites should complete the drug destruction form located on the NRG Oncology/RTOG web site www.rtog.org under _____ protocol-specific materials/regulatory resources and send the form to Biologics (see below for contact information).

Questions about supply and delivery should be directed to:

Elliott Lee, Clinical Research Program Manager
Biologics, Inc.
Clinical Research Services
120 Weston Oaks Court
Cary, NC 27513-2256
Email: elee@biologicsinc.com or clinicaltrials@biologicsinc.com
Phone: 919-459-4990 / Toll Free 800-693-4906
Fax: 919-256-0794

7.4 Cisplatin (7/29/13)

Refer to the package insert for detailed pharmacologic and safety information

- 7.4.1** Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH. Cisplatin also is available in vials containing 50mL or 100mL of a 1mg/mL solution.
- 7.4.2** Mechanism of Action: The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. This drug forms DNA adducts and cross-links.
- 7.4.3** Administration: After administering appropriate antiemetics, cisplatin will be infused over 1-2 hours along with vigorous hydration.
- 7.4.4** Storage and Stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.
- 7.4.5** Adverse Events: Human toxicity includes nausea, vomiting, anaphylaxis, neuropathies, ocular disturbances, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected.
- 7.4.6** Supply: Cisplatin is commercially available.

7.5 Etoposide (7/29/13)

Refer to the package insert for detailed pharmacologic and safety information

7.5.1 Formulation

For i.v. use, etoposide is supplied in 100-1000 mg vials at a concentration of 20 mg/ml. Each 100 mg vial also contains anhydrous citric acid 10 mg, benzyl alcohol 150 mg polysorbate 80 purified 400 mg, polyethylene glycol, and absolute alcohol. The manufacturer recommends etoposide dilution to a concentration of 0.2 or 0.4 mg/ml with either 0.9% Normal Saline, USP or 5% Dextrose Injection, USP. Diluted to these concentrations, it yields a product that is stable for 96 and 48 hours respectively, at room temperature (25°C), and under normal room fluorescent light in both glass and plastic containers.

7.5.2 Administration: Intravenous on days 1-5 every 4 weeks for 2 cycles; infuse etoposide over at least 45-60 minutes. Infusions of 30 minutes or less greatly increase the risk of hypotension.

7.5.3 Storage: Store intact vials at 15°C to 30°C (59°F to 86°F). Protect from light.

7.5.4 Adverse Events

Hematologic Toxicity: Myelosuppression is dose related and dose limiting with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20. Acute myeloid leukemia has been reported in rare instances.

Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. Nausea and vomiting can usually be controlled with standard antiemetic therapy.

Hypotension: Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted.

Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea and hypotension have been reported to occur in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the drug and to the administration of pressor agents, corticosteroids, antihistamines or volume expanders as appropriate. One fatal acute reaction associated with bronchospasm has been reported.

Alopecia: Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients.

Other Toxicities: The following adverse reactions have been infrequently reported: aftertaste, hypertension, rash, fever, pigmentation, pruritus, abdominal pain, constipation, dysphagia, transient cortical blindness, and a single report of radiation recall dermatitis.

7.5.5 Supply: Etoposide is commercially available.

7.6 Paclitaxel (7/29/13)

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

7.6.1 Paclitaxel is a poorly soluble plant product from the western yew, *Taxus brevifolia*. The injection is a clear, colorless to slightly yellow viscous solution. Improved solubility requires further dilution with either 0.9% sodium chloride or 5% dextrose in water. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours at ambient temperature (27°C).

7.6.2 Preparation

Paclitaxel injection is a sterile solution concentrate, 6 mg/ml in 5, 16.7, and 50 ml vials (30, 100, and 300 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. Paclitaxel will be diluted to a final concentration of 0.3 to 1.2 mg/ml in D₅W, NS, or D₅NS, 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.

7.6.3 Administration

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

Paclitaxel, at the appropriate dose and dilution, will be given as an infusion as per standard of care guidelines. The paclitaxel is administered using an in-line filter with a maximum size of 0.22 micron. 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.

7.6.4 Storage

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

7.6.5 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

7.6.6 Supply

Paclitaxel is commercially available.

7.7 **Carboplatin (7/29/13)**

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

7.7.1 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. Carboplatin also is available as a 10 mg/mL solution in 50, 150, and 450 mg vials.

7.7.2 Dose Calculation

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

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

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

7.7.3 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.

7.7.4 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.

7.7.5 Administration

Carboplatin will be infused intravenously as per standard of care guidelines. The dose of carboplatin is area under the curve (AUC) = 2.

7.7.6 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.

7.7.7 Supply

Carboplatin is commercially available.

7.8 **Clinical Trials Agreement**

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") 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/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing 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 (an)other Agent(s), 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 NCI, 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 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 Agent.
 3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). 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 Collaborator(s) 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 Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) 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:

E-mail: ncicteppubs@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.

7.9 Dose Modifications (6/26/15)
7.9.1 Arm 3: Patients in ALK Rearrangement Cohort

These patients are randomized to receive 12 weeks of induction with crizotinib. The following table should be used when reducing crizotinib doses for toxicity. Missed/vomited doses should not be made up but should be recorded in the comments section of the Medidata Rave drug form. There will be no dose reduction of crizotinib below dose level -2.

Dose Level	Dose of crizotinib
0 (starting dose)	250 mg BID
-1	200 mg BID
-2	250 mg daily

The grades of adverse events below refer to CTCAE, v. 4.

- Ocular Toxicity

For \geq grade 2 new or worsening eye pain, interrupt crizotinib until pain resolves to \leq grade 1, and then resume at the previous dose. If after 14 days the eye pain does not resolve to \leq grade 1, discontinue crizotinib.

For \geq grade 2 keratitis, discontinue crizotinib.

For \geq grade 2 ocular surface disease (conjunctivitis), interrupt crizotinib until toxicity improves to \leq grade 1. Once the conjunctivitis resolves to \leq grade 1, resume and reduce the dose by 50 mg/day.

- GI Toxicity: Nausea, Diarrhea, and/or Vomiting

Grade 1 or 2: Continue crizotinib at the same dose level and institute treatment for diarrhea (loperamide at 4mg at the first onset, followed by 2 mg every 2-4 hours until diarrhea free for 12 hours) and/or oral emetic therapy of physician's choice for nausea/vomiting. If grade 2 toxicity persists over 48-72 hours despite optimal medical management, decrease crizotinib by 1 dose level.

Grade 3: Hold crizotinib and institute treatment for diarrhea (loperamide at 4mg at the first onset, followed by 2 mg every 2-4 hours until diarrhea free for 12 hours) and/or oral emetic therapy of physician's choice for nausea/vomiting. Once toxicity resolves to \leq grade 2, resume with one dose level reduction. If crizotinib is held for \geq 21 days, discontinue crizotinib.

Grade 4: Discontinue crizotinib.

- Hematologic Toxicity

The ANC must be \geq 1,000/mcl and platelet count must be \geq 100,000/mcl on day 1 of each cycle for treatment to continue. Treatment with crizotinib may be delayed for up to 2 weeks for neutropenia and/or thrombocytopenia. If counts do not return to these levels within 2 weeks patients must discontinue therapy.

Patients developing febrile neutropenia of any duration must be dose reduced to dose level -2 for the subsequent cycle

- Pulmonary Toxicity

Patients with worsening pulmonary symptoms including new onset of or worsening dyspnea, cough or fever should be promptly evaluated for interstitial pneumonitis and treated as clinically indicated, including the use of corticosteroids.

Crizotinib should be held pending diagnosis of the pulmonary disorder, and discontinued if a diagnosis of interstitial pneumonitis is confirmed.

- Hepatic Toxicity

Give the following doses for crizotinib only:

SGOT (AST)		Bilirubin	Crizotinib
≤ 5 x ULN	and	≤ 3 x ULN	Same dose level
> 5 x ULN	or	> 3 x ULN	Hold*

*Hold crizotinib until AST ≤ 5 x ULN and bilirubin ≤ 3 x ULN, then resume treatment at one dose level lower. If crizotinib is held for ≥ 14 days, discontinue crizotinib therapy.

- Other Toxicities

Grade 3: Hold crizotinib until toxicity resolves to ≤ grade 2, then resume with a one dose level reduction. If crizotinib is held ≥ 21 days, discontinue crizotinib.

Grade 4: Discontinue crizotinib.

7.9.2 Arm 1: Patients in EGFR TK Mutation Cohort

These patients are randomized to receive 12 weeks of induction with erlotinib. The recommended dose of single-agent erlotinib is 150 mg/day. Missed/vomited doses should not be made up but should be recorded in the comments section of the Medidata Rave drug form.

For toxicity that is thought to be related to erlotinib, the daily dose of erlotinib will be decreased according to the schedule displayed in the Table 1.

- Patients with unresolved toxicity after 2 weeks should be taken off study. However, if it is the treating physician's opinion that the patient may benefit from continued treatment, the patient may continue on study.
- Patients may have a second dose reduction for toxicity; however, patients requiring a third dose reduction should be taken off study unless, in the opinion of the treating physician, there is reason to believe the patient may benefit from continued treatment.
- Once a dose has been reduced for a patient, it should not be subsequently increased.

Table 1: Erlotinib Dose Level Reduction

Starting Dose	Dose (-1)	Dose (-2)	Dose (-3)
150 mg/day	100 mg/day	75 mg/day	50 mg/day

Table 2: Erlotinib Dosage Modification Criteria for Erlotinib-Related Toxicities

Toxicity	Grade	Erlotinib dosage modification*	Guideline for management
Keratitis	1	None	No intervention
	2 (if ≤ 14 days)	None	Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks
	2 (if > 14 days)	Hold until recovery to \leq grade 1 <u>And then</u> Reduce 1 dose level	
≥ 3	Hold until recovery to \leq grade 1 And then Reduce 1 dose level*		
Diarrhea	1	None	No intervention
	2	<ul style="list-style-type: none"> • None if tolerable • If not tolerable, hold until resolution to grade ≤ 1, then resume at the same dose. • If intolerable grade 2 recurs after resumption, hold until resolution to grade ≤ 1 and resume with 1 dose reduction. 	Loperamide (4 mg at first onset, followed by 2 mg every 2–4 hrs until diarrhea free for 12 hrs)
	≥ 3 (despite optimal loperamide use)	Hold until recovery to \leq grade 1 <u>And then</u> Reduce 1 dose level*	
Rash	1	None	
Rash	2	<ul style="list-style-type: none"> • None if tolerable • If not tolerable, hold until resolution to grade ≤ 1, then resume at the same dose. • If intolerable grade 2 recurs after resumption, hold until resolution to grade ≤ 1 and resume with 1 dose reduction. 	Any of the following: minocycline ⁺ , topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)
	≥ 3	Hold until recovery to \leq grade 1 <u>And then</u> Reduce 1 dose level	

Toxicity	Grade	Erlotinib dosage modification*	Guideline for management
Bilirubin	(for patients without pre-existing liver dysfunction) 3 x ULN	Withhold erlotinib. Discontinue if levels do not improve significantly or resolve within three weeks.	
	(for patients <u>with</u> pre-existing liver dysfunction) ≥2 x baseline		
Liver trans-aminase	(for patients without pre-existing liver dysfunction) ≥5 x ULN	Withhold erlotinib Discontinue if levels do not improve significantly or resolve within three weeks.	
	(for patients <u>with</u> pre-existing liver dysfunction) ≥3 x baseline		
Signs and symptoms of interstitial pneumonitis		Hold pending diagnosis Permanently discontinue if diagnosis is confirmed and considered possibly related to erlotinib	Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated
Other toxicity	≥2 prolonged clinically significant toxicity	Hold until recovery to ≤ grade 1 <u>And then</u> Reduce 1 dose level*	Treatment as appropriate
*if dose has been previously held for grade 2 rash or diarrhea, and grade 2 symptoms recur, OR if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce dose one level			

Additional erlotinib dose modification guidelines include:

Discontinue erlotinib for:

- Severe hepatic toxicity that does not improve significantly or resolve within three weeks.
- Gastrointestinal perforation.
- Severe bullous, blistering or exfoliating skin conditions.
- Corneal perforation or severe ulceration.

Withhold erlotinib:

- For severe (grade 3 to 4) renal toxicity, and consider discontinuation of erlotinib.
- For acute/worsening ocular disorders such as eye pain, and consider discontinuation of erlotinib.

Reduce erlotinib by 50 mg decrements:

- If severe reactions occur with concomitant use of strong CYP3A4 inhibitors (such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin [TAO], voriconazole, or grapefruit or grapefruit juice) or when using concomitantly with an inhibitor of both CYP3A4 and CYP1A2 (e.g., ciprofloxacin). Avoid

- concomitant use if possible.
- When restarting therapy following withholding treatment for a dose-limiting toxicity that has resolved to baseline or grade ≤ 1 .

Increase erlotinib by 50 mg increments as tolerated for:

- Concomitant use with CYP3A4 inducers, such as rifampin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, or St. John’s wort. Increase doses by 50 mg increments at 2-week intervals to a maximum of 450 mg. Avoid concomitant use, if possible.
- Concurrent cigarette smoking. Increase by 50 mg increments at 2-week intervals to a maximum of 300 mg. Immediately reduce the dose of erlotinib to the recommended dose (150 mg or 100 mg daily) upon cessation of smoking.

Drugs affecting gastric pH

- Avoid concomitant use of erlotinib with proton pump inhibitors if possible. Separation of doses may not eliminate the interaction since proton pump inhibitors affect the pH of the upper gastrointestinal (GI) tract for an extended period.
- If treatment with an H2-receptor antagonist such as ranitidine is required, erlotinib must be taken 10 hours after the H2-receptor antagonist dosing and at least 2 hours before the next dose of the H2-receptor antagonist.
- Although the effect of antacids on erlotinib pharmacokinetics has not been evaluated, the antacid dose and the erlotinib dose should be separated by several hours, if an antacid is necessary.

7.9.3 Arms 2 and 4: For Both Cohorts Receiving Concurrent Chemotherapy and Radiation (6/26/15)

The grades of adverse events below refer to CTCAE, v. 4.

Cisplatin (50 mg/m²) on Days 1 and 8 and Etoposide (50 mg/m²) on Days 1-5 administered intravenously q4 weeks for 2 cycles

If dose reduction is required during chemoradiation, no re-escalation is allowed in subsequent chemoradiation cycles.

If cisplatin and/or etoposide are held for greater than 2 consecutive weeks, the drugs will be held permanently for the duration of concurrent therapy.

The following dose levels are used for dose modifications during both the concurrent chemoradiation phase. Missed/vomited doses should not be made up but should be recorded in the comments section of the Medidata Rave drug form. There will be no dose reduction below level -1.

Dose Level	Cisplatin	Etoposide
0	50 mg/m ²	50 mg/m ²
-1	40 mg/m ²	40 mg/m ²

- Hematologic Toxicity

Dose modification on d1 of a new cycle during concurrent chemoradiation (cycles 1-4)

ANC		Platelet	Cisplatin and Etoposide Dose
$\geq 1,000/\text{mcl}$	and	$\geq 100,000/\text{mcl}$	Continue w/ previous dose
$< 1,000/\text{mcl}$	or	$< 100,000/\text{mcl}$	Hold*

*Check weekly and resume therapy at previous dose (no dose reduction) when counts recover to ANC $\geq 1,000$ and platelets $\geq 100,000/\text{mcl}$.

Febrile neutropenia occurring during chemoradiation will result in a decrease of the cisplatin and etoposide dose level by –1. Febrile neutropenia occurring despite dose reduction during chemoradiation will result in discontinuation of chemotherapy. Radiation therapy is held for neutropenia (ANC < 500/mcl); radiation therapy may be restarted when the ANC ≥ 500/mcl.

- **Renal Toxicity**

Based on day 1 of each cycle for cisplatin and etoposide:

CrCl < 50 ml/min	Hold therapy. Administer fluids and repeat creatinine in one week.
If after one week CrCl ≥ 50 ml/min	Administer both cisplatin and etoposide at full dose.
If after one week CrCl < 50 ml/min	Discontinue chemotherapy.

- **Hepatic Toxicity**

Give the following doses for etoposide only:

Bilirubin	Etoposide
< 1.5 mg/dl	Same dose level
1.5 -3.0 mg/dl	↓ 1 dose level
≥ 3.0 mg/dl	Hold*

- **Gastrointestinal Toxicity**

Nausea/Vomiting: For ≥ grade 3 nausea or vomiting despite maximum antiemetics, decrease cisplatin by one dose level for the next dose. If nausea and vomiting improve, cisplatin dose should be re-escalated to the previous dose, if possible.

- **Neurotoxicity (Peripheral)**

Cisplatin doses should be modified for neurologic toxicity (see below). Serum magnesium and calcium levels should be checked; vitamin B12 levels may need to be evaluated especially in older patients.

Grade 1: Give cisplatin at full dose.

Grade ≥ 2: Hold cisplatin until neurotoxicity resolves to ≤ grade 1, then resume with one dose level reduction. Continue treatment with etoposide. If cisplatin is held for ≥ 21 days, discontinue cisplatin.

- **Ototoxicity:** Discontinue cisplatin for ≥ grade 3 ototoxicity.

- **Hypomagnesemia and Hypokalemia:** is not an indication for stopping therapy. Oral and parenteral supplementation is indication for serum levels < LLN.

- **All Other Treatment-Related Toxicities that Exceed grade 2:** (except alopecia, nausea, vomiting, fatigue and anorexia), hold cisplatin and etoposide until the toxicities have resolved to grade 2 or less and resume cisplatin and etoposide with one dose level reduction.

Paclitaxel (50 mg/m²) and Carboplatin (AUC-2) intravenously weekly during thoracic radiation for 6 weeks followed 4-6 weeks later by 2 cycles of Paclitaxel (200 mg/m²) and Carboplatin (AUC-6) intravenously q 3 weeks for 2 cycles

If dose reduction is required during chemoradiation, no re-escalation is allowed in subsequent chemoradiation cycles. However, paclitaxel and carboplatin will be started at dose level 0 after the completion of radiation therapy.

If paclitaxel and/or carboplatin are held for greater than 2 consecutive weeks, the drugs will be held permanently for the duration of concurrent therapy.

The following dose levels are used for dose modifications during both the concurrent chemoradiation phase. There will be no dose reduction below level -1.

Dose Level	Paclitaxel	Carboplatin
0	50 mg/m ²	AUC = 2
-1	40 mg/m ²	AUC = 1

The following dose levels are used for dose modifications during the consolidation phase. There will be no dose reduction below level -1.

Dose Level	Paclitaxel	Carboplatin
0	200 mg/m ²	AUC = 6
-1	150 mg/m ²	AUC = 4.5

- Hematologic Toxicity

Dose Modification during Concurrent Chemoradiation:

ANC		Platelet	Carboplatin and Paclitaxel Dose
≥ 1,000/mcl	and	≥ 100,000/mcl	Continue w/ previous dose
< 1,000/mcl	or	< 100,000/mcl	Hold*

*Check weekly and resume therapy at previous dose (no dose reduction) when counts recover to ANC ≥ 1,000 and platelets ≥ 100,000/mcl. If, after 3 weeks of holding drugs ANC < 1,000/mcl or platelet < 100,000/mcl, contact Drs Govindan, Hahn, or Tsao.

Febrile neutropenia occurring during chemoradiation will result in a decrease of the carboplatin and paclitaxel dose level by -1. Febrile neutropenia occurring despite dose reduction during chemoradiation will result in discontinuation of carboplatin, but continuation of paclitaxel at the previous dose (-1 dose level). Radiation therapy is held for neutropenia (ANC < 500/mcl); radiation therapy may be restarted when the ANC ≥ 500/mcl.

Dose Modification on Day 1 of a New Cycle during Consolidation Therapy:

ANC		Platelet	Chemotherapy
≥ 1,000/mcl	and	≥ 100,000/mcl	Continue w/ previous dose
< 1,000/mcl	or	< 100,000/mcl	Hold*

*Check weekly and resume therapy at previous dose (no dose reduction) when counts recover to ANC ≥ 1,000 and platelets ≥ 100,000/mcl. If, after 3 weeks of holding drugs ANC < 1,000/mcl or platelet < 100,000/mcl, contact the Drs. Govindan, Hahn, or Tsao.

Febrile neutropenia occurring during consolidation will result in a decrease of both the carboplatin and paclitaxel doses by 1 dose level.

- Renal Toxicity: There are no dose modifications for renal toxicity. It is not necessary to change the dose of carboplatin unless the calculated dose changes by ≥ 10%.

- **Neurotoxicity (Peripheral)**
Paclitaxel doses should be modified for neurologic toxicity (see below). Serum magnesium and calcium levels should be checked; folate and vitamin B12 levels may need to be evaluated especially in older patients.

Grade 1: Give paclitaxel at full dose.

Grade ≥ 2: Hold paclitaxel until neurotoxicity resolves to ≤ grade 1, then resume with one dose level reduction. Continue treatment with carboplatin. If paclitaxel is held for ≥ 21 days, discontinue paclitaxel, but continue treatment with carboplatin.

- **Hepatic Toxicity:**
Give the following doses for paclitaxel only:

SGOT (AST)		Bilirubin	Paclitaxel
≤ 2.5 x ULN	and	< 1.5 mg/dl	Same dose level
2.5 – 5.0 x ULN	and	< 1.5 mg/dl	↓ 1 dose level
> 5 x ULN	or	≥ 1.5 mg/dl	Hold*

*Hold paclitaxel until AST ≤ 5 x ULN and bilirubin < 1.5 mg/dl, then resume treatment at one dose level lower. (Continue treatment with carboplatin. If paclitaxel is held for ≥ 21 days, discontinue paclitaxel therapy (continue treatment with carboplatin).

- **Hypersensitivity to Carboplatin**
Grade 1: Slow the infusion until symptoms resolve, then restart the infusion at the initial planned rate.

Grade 2: Stop the infusion. Administer H1 and/or H2 blockers +/- dexamethasone, according to physician discretion/institutional guidelines. Restart carboplatin when symptoms resolve and pretreat before all subsequent doses of carboplatin.

Grade 3 or 4: Patient should be removed from all protocol therapy.

- **Hypersensitivity to Paclitaxel**
Grade 1: Slow the infusion until symptoms resolve, then restart the infusion at the initial planned rate.

Grade 2: Stop the infusion. Administer H1 and/or H2 blockers +/- dexamethasone according to physician discretion/institutional guidelines. Restart when symptoms resolve and pretreat before all subsequent doses.

Grade 3 or 4: Discontinue therapy with paclitaxel.

- **All Other Treatment-Related Toxicities that Exceed grade 2:** (except alopecia, nausea, vomiting, fatigue and anorexia), hold paclitaxel and carboplatin until the toxicities have resolved to grade 2 or less and resume carboplatin and paclitaxel with one dose level reduction.

7.10 Modality Review

The Alliance Co-Principal Investigator/Medical Oncologist, Ramaswamy Govindan, MD, and the NRG Oncology and Alliance Medical Oncology Co-Chairs, Anne Tsao, MD, and Olwen Hahn, 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, Unacceptable Deviation, 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.

Drs. Govindan, Tsao, and Hahn will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. They will perform the next review after complete data for the next 20 cases enrolled has 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 has been received at NRG Oncology, whichever occurs first.

7.11 **Adverse Events (5/29/14)**

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (the CTEP Adverse Event Reporting System) application accessed via either the CTEP web site (<https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613>).

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Operations Office at 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.

7.11.1 **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. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf]

7.11.2 **Serious Adverse Events (SAEs)** — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.12 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.12. **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. **7.11.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)**

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS 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.

7.12 CTEP-AERS Expedited Reporting Requirements (5/29/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event 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 the NRG Oncology Operations Office at 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 an 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 a 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 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 allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials conducted under an IND as described in the table below. Please refer to the erlotinib SPEER for exclusions to expedited reporting. **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 Arm 1 under an IND/IDE for Erlotinib 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:				
<ol style="list-style-type: none"> 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.				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	
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				
<u>Expedited AE reporting timelines are defined as:</u>				
<ul style="list-style-type: none"> ○ “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. 				

¹Serious 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.

Effective Date: May 5, 2011

(5/29/14) Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND

The following are protocol-specific exceptions to expedited reporting via CTEP-AERS. Report the following AEs in an expedited manner only if the AEs exceed grade 2 (CTCAE, v. 4): Esophagitis, dysphagia.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials utilizing commercial agents as described in the table below. Please refer to the additional instructions or exceptions to expedited reporting immediately following 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 Utilizing Commercially Available Agents within 30 Days of the Last Administration of the Commercial Agent ^{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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
-----------------	--------------------	--------------------	--------------------	------------------------

Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days		24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	
<p><u>Expedited AE reporting timelines are defined as:</u></p> <ul style="list-style-type: none"> ○ “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. 			
<p>¹Serious 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:</p> <p>Expedited 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 4, and Grade 5 AEs <p>Expedited 10 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events <p>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.</p> <p>Effective Date: May 5, 2011</p>			

(5/29/14) Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP-IND

The following are protocol-specific exceptions to expedited reporting via CTEP-AERS. Report the following adverse events (AEs) in an expedited manner only if the AEs **exceed** grade 3 (CTCAE, v. 4): Nausea, vomiting, diarrhea, and dehydration. Report the following AEs in an expedited manner only if the AEs **exceed** grade 2 (CTCAE, v. 4): Esophagitis, dysphagia.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication. Herbal and nutritional supplements are allowed, provided they do not interact with the CYP34A pathway.

9.2 Non-permitted Supportive Therapy

During concomitant chemoradiation, hematopoietic growth factors are contraindicated.

10.0 TISSUE/SPECIMEN SUBMISSION (6/26/15)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as the optional tissue/specimen submission for banking and translational research.

If the patient consents to participate in the tissue/specimen component of the 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/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission (6/26/15)

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. The NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank – San Francisco provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. **Note:** The NRG Oncology Biospecimen Bank – San Francisco will provide collection kits and instructions at no charge for the submission of specimens in this protocol.

In this study, **it is required that each enrolling institution screen the patient's tissue for at least EGFR TK domain (exon 19 deletion, L858, and T790M) mutation and EML4-ALK fusion arrangement (must be done in a CLIA certified lab).** The enrolling institution also must document the method of testing and the specific result and submit 5 unstained slides (5 micron thickness) to the NRG Oncology Biospecimen Bank – San Francisco for retrospective central review and biomarker analyses. Once all patients have been enrolled, these specimens will be used for EGFR and ALK testing, performed using a uniform diagnostic assay (the specific assay will be determined at a future date, as it may evolve during the course of this trial).

For the institution's EGFR mutation testing, any genotyping method to detect exon 19 deletion or L858R mutation may be used as long as it is performed in a CLIA certified laboratory. **Note:** The enrolling institution must provide the method of testing and the specific result to the Biospecimen Bank (i.e. specific mutation).

For the institution's ALK testing, the FDA approved Vysis dual color FISH assay must be used for the detection of an ALK rearrangement. **Note:** The enrolling institution must provide the testing laboratory and the specific result (% of positive cells).

In addition, it is **highly recommended** (but optional) that archival tissues and blood specimens be submitted to the NRG Oncology Biospecimen Bank for banking for future translational research. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for approved studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

10.2 Tissue Submission for Retrospective Central Review of Biomarker Screening: Mandatory (6/26/15)

All patients must consent to pre-entry biomarker screening of tissue for EGFR mutation analysis and ALK fusion arrangement by the enrolling institution (must be done in a CLIA certified lab).

The institution must provide the following material to the NRG Oncology Biospecimen Bank – San Francisco for retrospective central review of biomarker screening within 42 calendar days of enrolling the patient:

10.2.1 One H & E stained slide per positive biopsy site (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide);

- 10.2.2** Five 5 micron unstained sections cut onto positive charged slides; The slides must correspond to one of the H&Es being submitted and must be clearly labeled with the pathology identification number that corresponds to the Pathology Report and the block id.
- 10.2.3** A Pathology Report documenting that the submitted slides contain tumor; the report must include the NRG Oncology protocol number and the patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and date of procedure information must NOT be removed from the report.
- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.
- 10.2.4** A Specimen Transmittal (ST) Form stating that the tissue is being submitted for central review and biomarker analysis. The Form must include the NRG Oncology protocol number, the patient's case number, the method used by the institution for biomarker screening, and the specific result.
- 10.2.5** Retrospective central review of EGFR TK domain mutations and EML4-ALK fusion arrangement will be performed by the Pathology Co-Chair, Dr. Jones for patients who have been enrolled to the study.

10.3 Specimen Collection for Tissue Banking and Translational Research: Highly Recommended (but Optional) (6/26/15)

For patients who have consented to participate in the tissue/blood component of the study (See sample consent).

Patients must be offered the opportunity to participate in the tissue/specimen collection for banking and translational research. If the patient consents to participate in this component, the site is required to submit the patient's specimens as specified below. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent form.

See [Section 1.4](#) for the proposed translational research studies for this trial.

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

- 10.3.1** One H&E stained slide ((slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide)
- 10.3.2** Corresponding paraffin-embedded tissue block (the block must match the H&E being submitted) or two 3 mm punch biopsies embedded in a new paraffin block along with a corresponding H&E slide of the punch block. Fifteen 5 micron unstained slides are acceptable for sites unable to submit blocks/punches.

Note: A kit with the punch, tube, and instructions can be obtained free of charge from the NRG Oncology Biospecimen Bank. Block, core or slides must be clearly labeled with the pathology accession number and block id that corresponds to the Pathology Report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.
- 10.3.3** A Pathology Report documenting that the submitted block or core 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.
- 10.3.4** A Specimen Transmittal Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank- San Francisco; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.
- 10.3.5** Serum, Plasma, Whole Blood (see [Appendix IV](#) for collection, processing, and kit information) Prepaid labels are provided with kits. Kits can be requested from NRGBB@ucsf.edu. The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the NRG Oncology

protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.]

10.3.6 Storage Conditions

Store frozen specimens 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).

OR:

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

OR:

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

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

10.3.7 Specimen Collection Summary:

Specimens for Central Review of Biomarker Screening (Mandatory)			
Specimens taken from patient:	Collected when:	Submitted as:	Shipped:
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
Five 5 micron unstained sections cut onto positive charged slides	Pre-treatment	Five 5 micron unstained sections cut onto positive charged slides	Slides shipped ambient. (with a cold pack during summer)
Specimens for Banking/Translational Research (Recommended)			
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide (can be additional or same as mandatory central review specimens listed above)	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or two 3 mm diameter core of tissue, punched from the tissue block with a punch tool embedded in paraffin	Pre-treatment	Paraffin-embedded tissue block or two 3mm punch biopsies embedded in paraffin Note: 15 unstained slides are acceptable for sites unable to submit blocks/punches (can be additional or same as Central Review specimens)	Block or punch shipped ambient (with a cold pack during summer)
SERUM: 5-10 mL of whole blood in red top tube and centrifuge	Pre-treatment	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to eight)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pre-treatment	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to eight)	Plasma sent frozen on dry ice via overnight carrier
Whole blood for DNA: 5-10 mL of anticoagulated	Pre-treatment	Frozen whole blood samples containing 1	Whole blood sent frozen on dry ice via

whole blood in EDTA tube #2 (purple/ lavender top) and mix	Note: If site missed this collection time point, the site may collect whole blood for DNA at a later time point but must note this on the ST Form.	ml per aliquot in 1ml cryovials (three to five)	overnight carrier
--	--	---	-------------------

10.3.8 Submit materials for Central Review, Tissue Banking, and Translational Research as follows:

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

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.4 Reimbursement (5/29/14)

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

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 tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. 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 for a summary of assessments and time frames. See the section below for details of evaluations and exceptions.

11.2 Details of Evaluations (6/26/15)

11.2.1 Pre-treatment Evaluation

- Tumor measurements: Measure in at least 1 dimension and record the longest dimension as ≥ 10 mm with CT scan of the chest and upper abdomen.
- History and physical examination must include recording of pulse, BP, weight, and body surface area.
- A CT scan with contrast of the chest and upper abdomen to include liver and adrenals is required unless medically contraindicated.
- A CT scan of the brain with contrast can be substituted if an MRI of the brain with contrast is medically contraindicated.

- Nutritional assessment should include evaluation of the need for prophylactic gastrostomy tube placement if the patient is $\geq 10\%$ below ideal body weight or is unable to swallow pills.

11.2.2 Evaluation During Treatment

- Tumor measurements: Measure in at least 1 dimension and record the longest dimension as ≥ 10 mm with CT scan of the chest and upper abdomen.
- History and physical examination must include recording of pulse, BP, weight and body surface area. Note: It is not necessary to change drug doses due to changes in the patient's body surface area unless the calculated dose changes by $\geq 10\%$.
- For patients on Arms 1 and 3: a CT scan of the chest and upper abdomen should be completed after 6 weeks of oral induction therapy and at the completion of oral induction therapy.
- Patients on Arms 1 and 3 should have a CBC, platelets, serum creatinine, bilirubin, AST/ALT, alkaline phosphatase every 3 weeks during erlotinib or crizotinib.
- Patients receiving paclitaxel and carboplatin should have a CBC, platelets, serum creatinine, and bilirubin weekly.
- Patients receiving paclitaxel and carboplatin should have a CT scan of the chest and upper abdomen 4-6 weeks after completion of chemoradiation. This should occur prior to consolidation chemotherapy.
- Patients receiving cisplatin and etoposide should have a CBC, platelets, and serum creatinine on weeks 1, 2, 5, and 6.
- For patients on Arms 1 and 3: Weekly adverse event evaluations may be done over the phone by the study nurse/CRA.

11.2.3 Evaluation in Follow Up

- History and physical examination must include recording of pulse, BP, weight and body surface area.
- All patients: A CT scan of the chest and upper abdomen should be completed 4-6 weeks after completion of chemoradiation therapy.
- All patients: After the first follow-up scan obtained 4-6 weeks after completion of chemoradiation therapy, a CT scan of the chest and upper abdomen should be completed every 3 months for 2 years, every 6 months for 3 years, then annually.
- For patients on Arms 2 and 4: Adverse event evaluations 2 months after completion of therapy may be done over the phone by the study nurse/CRA.

11.3 **Measurement of Response**

Response will be evaluated in this study using the revised RECIST guideline, v. 1.1 [European Journal of Cancer. 45: 228-247, 2009] will be used as a guideline to determine study eligibility. See http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf for further details.

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

- **Measurable disease** - the presence of at least one measurable lesion; If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- **Non-measurable lesions** - All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: pleural or pericardial effusion, lymphangitic involvement of lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

Response Criteria: Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions; Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

11.4 Measurement/Definition of Progression/Recurrence

Progression is defined as changes in known lesions that are not related to post-chemoradiation-induced inflammation, as defined below:

- At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study); in addition to the relative increase of 20%, the sum also must demonstrate an absolute increase of at least 5 mm.
- Appearance of ≥ 1 new lesions also is considered progression.
- Local progression is defined as progression within the PTV.
- Regional progression is defined as progression outside of the PTV but within the same lobe of the lung as the primary tumor or in regional lymph nodes as defined by the AJCC 7th edition nodal stations.
- Distant progression is defined as progression at any other site, including development of a malignant pleural or pericardial effusion.

11.5 Criteria for Discontinuation of Protocol Treatment

- Unacceptable toxicity; see [Section 6.0](#) and [Section 7.0](#) for further information.
 - Progression of disease;
 - Development of a 2nd primary upper aerodigestive tract malignancy (eg, lung cancer, esophagus cancer, 2nd primary head and neck cancer);
 - A delay in protocol treatment, as specified in Sections 6.0 and/or 7.0. Treatment breaks, if necessary, ideally should not exceed 5 treatment days at a time and 10 treatment days total.
- If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (5/29/14)

This study will utilize Medidata Rave® for remote data capture (RDC) of all data.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave, see Section 5.0 of the protocol.

Each person responsible for data entry must be on the NRG Oncology roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS (Regulatory Support System), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Once an account is activated, eLearning modules will be available for Rave RDC instructions. Please note, site users will not be able to access the study in Rave until

all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1 Summary of Data Submission (6/24/14)

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.

Folder	Form/Item
Registration via the OPEN System	<ul style="list-style-type: none"> • Subject Enrollment
Enrollment When pushed into RAVE there will be 4 forms representing registration	<ul style="list-style-type: none"> • Eligibility Checklist • Step Information • Treatment Assignment • Demography
Baseline	<ul style="list-style-type: none"> • Baseline Labs • Diagnostic Staging • Exclusion Criteria • Lymph Node Assessment • Pathology Report • Patient History (formerly known as the A5) • Work Up
RT Plan Upload	<ul style="list-style-type: none"> • Digital Data-(Upload of e-mail confirmation from TRIAD submission required)
Concomitant Medications	<ul style="list-style-type: none"> • Concomitant Medication (only required if patient is taking concomitant medications)
Week 3 (Induction)* Week 6 (Induction)* Week 9 (Induction)* Week 12 (Induction)* *Arms 1 and 3 only	<ul style="list-style-type: none"> • Any Adverse Events? • Adverse Events – if any adverse events? = ‘yes’ • Erlotinib – if enrolled to Arm 1 • Crizotinib – if enrolled to Arm 3 • On Treatment Labs • Patient Pill Diary—completed every 3 weeks by patient (print from RTOG web site) and uploaded to Crizotinib or Erlotinib form
Concurrent Treatment	<ul style="list-style-type: none"> • RT Administration • RT Treatment-if was radiation therapy given = ‘yes’ • RT Treatment Record- if was radiation therapy given = ‘yes’ (Upload of copy of Daily RT Treatment Chart required)

	<ul style="list-style-type: none"> • Any Adverse Events? • Adverse Events – if any adverse events? = 'yes' • Carboplatin (if selected during registration) • Paclitaxel (if selected during registration) • Cisplatin (if selected during registration) • Etoposide (if selected during registration) • On Treatment Labs 01 (up to 11 additional weeks may be added by user if needed)
<p>Consolidation Treatment*</p> <p>*Only appears if paclitaxel and carboplatin are selected during registration</p>	<ul style="list-style-type: none"> • Any Adverse Events? • Adverse Events – if any adverse events? = 'yes' • Carboplatin • Paclitaxel • On Treatment Labs 01 (up to 11 additional weeks may be added by user if needed)
<p>End of All Treatment</p>	<ul style="list-style-type: none"> • End of All Treatment (this form should be completed for all patients after their final day of all protocol treatment)
<p style="text-align: center;"><u>Year 1</u></p> <p>Follow Up 01 (month 1 post tx) Follow Up 02 (month 2 post tx) Follow Up 03 (month 3 post tx) Follow Up 04 (month 6 post tx) Follow Up 05 (month 9 post tx) Follow Up 06 (month 12 post tx)</p> <p style="text-align: center;"><u>Year 2</u></p> <p>Follow Up 07 (month 15 post tx) Follow Up 08 (month 18 post tx) Follow Up 09 (month 21 post tx) Follow Up 10 (month 24 post tx)</p> <p style="text-align: center;"><u>Years 3-5</u></p> <p>Follow Up 11 (month 30 post tx) Follow Up 12 (month 36 post tx) Follow Up 13 (month 42 post tx) Follow Up 14 (month 48 post tx) Follow Up 15 (month 54 post tx) Follow Up 16 (month 60 post tx)</p> <p style="text-align: center;"><u>Years 6-10</u></p> <p>Follow Up 17 (month 72 post tx) Follow Up 18 (month 84 post tx) Follow Up 19 (month 96 post tx) Follow Up 20 (month 108 post tx) Follow Up 21 (month 120 post tx)</p>	<ul style="list-style-type: none"> • Any Adverse Events? • Adverse Events – if any adverse events? = 'yes' • Patient Contacted • Follow-up - if Patient able to be Contacted = 'yes' • Disease Assessment- if Documented clinical assessment = 'yes' • New Primary Cancer- If New Primary Cancer= 'yes' • Non-Protocol Treatment- if non-protocol cancer therapy= 'yes' • Pulmonary Function Tests – if PFTs performed = 'yes' • Primary Cause of Death – If Vital Status = 'dead'
<p>CTEP-AERS</p>	<ul style="list-style-type: none"> • CTEP-AERS Upload Form – used by HQ to upload CTEP-AERS reports, sites have read only access to this folder/form
<p>Source Documentation</p>	<ul style="list-style-type: none"> • Source Documentation Upload – used by the sites in the event that source documentation needs to be uploaded to HQ

12.2 Summary of Dosimetry Digital Data Submission (5/29/14)

See Section 5.0 for TRIAD account access and installation instructions.

<u>Item</u>	<u>Due</u>
Preliminary Dosimetry Information	
Digital Data Submission – Treatment	Within 1 week of start of RT
Digital data submission includes the following, all in DICOM format:	
<ul style="list-style-type: none">• CT data, critical normal structures, all GTV, CTV, and PTV contours (CT Files, RT Structure File)	
<ul style="list-style-type: none">• Digital beam geometry beam sets (RT Plan File)	
<ul style="list-style-type: none">• Doses for concurrently treated beams (RT Dose File)	
<ul style="list-style-type: none">• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan• All required structures MUST be labeled per Table 6.5.6.• The “RTOG 1306 Datasheet” is available in the Forms section of the of the NRG Oncology/RTOG web site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1306. Submit via TRIAD with the digital data listed above.	
Upon submission of digital RT data via TRIAD, complete an online Digital Data Submission Form (DDSI Form), found on the NRG Oncology/RTOG web site under the ‘Core Lab’ section, http://www.rtog.org/CoreLab/TRIAD.aspx	
Note: All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.)	

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

13.1.1 Progression-free survival (PFS); failure is defined as occurrence of local or regional progression, distant metastases, or death from any cause from the time of randomization to the occurrence of one of the failure events, whichever occurs first.

13.2 Secondary Endpoints

13.2.1 Evaluation of response rates;

13.2.2 Grade 3-5 (CTCAE, v. 4) adverse events;

13.2.3 Overall survival (OS); failure is defined as death from any cause.

13.2.4 Other progression-related endpoints, such as local-regional progression, distant progression;

13.2.5 Correlation between clinical outcomes and tumor molecular aberrations identified from deep sequencing of selected kinomes in patients from whom adequate baseline tissue is available.

13.3 Sample Size

The primary objective of this randomized phase II trial is to assess whether patients with unresectable stage III NSCLC treated with individualized therapy based on molecular characteristics have a longer progression-free survival (PFS) than those treated with standard care therapy alone. Only patients with EGFR TK mutation or EML4-ALK fusion rearrangement will be enrolled and randomized 1:1 to a standard arm (Arm 2 if EGFR cohort; Arm 4 if ALK cohort) or experimental arm (Arm 1 if EGFR cohort; Arm 3 if ALK cohort). Patients with both the EGFR mutation and ALK arrangement will be placed in the ALK Cohort. Patients will be stratified by weight loss ($\leq 5\%$ vs. $> 5\%$), stage (IIIA vs. IIIB), and chemotherapy (cisplatin and etoposide vs. paclitaxel and carboplatin). On the standard arm, patients will be treated with a combination of

chemotherapy and thoracic radiation. On the experimental arm, patients with EGFR mutation will be treated with erlotinib followed by concurrent chemotherapy and radiation, and patients with ALK translocation will be treated with crizotinib followed by concurrent chemotherapy and radiation. PFS is defined as the time from randomization to first documentation of progression or death due to any cause. Patients last known to be alive and progression free are censored at the date of last clinical assessment. For both EGFR mutation and ALK translocation cohorts, the PFS rates for the standard arms, as well as the rates of non-analyzable (if any) may be carefully monitored and re-estimated at interim analysis if needed.

The total number of patients to be randomized is 148 for the EGFR mutation cohort and 74 for the ALK translocation cohort. Taking into account 5% of registered patients who are deemed ineligible and withdraw from the study before randomization, **we plan to enroll approximately 156 patients to the EGFR mutation cohort and 78 patients to the ALK translocation cohort.**

13.3.1 Sample Size Justification for the EGFR Mutation Cohort

The goal is to determine the PFS superiority of the experimental therapy relative to the standard therapy. In CALGB 30407 (the immediate preceding study conducted by CALGB in IIIA or IIIB unresectable NSCLC), the median PFS is approximately 12 months for patients on the 2 trial arms (chemoradiation and chemoradiation plus cetuximab). This trial aims to demonstrate a 65% improvement in median PFS, or 19.8 months, for the patients with an EGFR mutation on experimental therapy compared to patients with an EGFR mutation on standard therapy. Assuming constant hazards (exponential survival times), these median PFS times for patients with an EGFR mutation on experimental therapy (E1) and patients with an EGFR mutation on standard therapy (E2) correspond to a hazard ratio $\lambda_{E1}/\lambda_{E2} = 0.606$ (40% relative hazard reduction). A design with 90% power and one-sided 15% type I error rate would require 89 progression events to detect this effect size. Assuming approximately uniform accrual of 6 patients per month over a 25-month period, this would result in 148 EGFR mutation patients (74 per arm). The required 89 progression events for the superiority test will be observed within 1 additional year of follow up after accrual completion.

13.3.2 Sample Size Justification for the ALK Cohort

The goal is to determine the PFS superiority of the experimental therapy relative to the standard therapy. In CALGB 30407, the median PFS is about 12 months for patients on the 2 trial arms. This trial aims to demonstrate that there is a 65% improvement in median PFS, or 19.8 months, for patients with an EML4-ALK translocation on experimental therapy relative to the same group of patients on standard therapy. Under constant hazards (exponential survival times), this median PFS times for patients with EML4-ALK translocation on experimental therapy (A1) and the same group of patients on standard therapy (A2) correspond to a hazard ratio $\lambda_{A1}/\lambda_{A2} = 0.606$. A design with 80% power and one-sided 15% type I error rate would require 58 progression events to detect the specified hazard ratio. Assuming approximately uniform accrual of 3 patients per month over a 25-month period, for a total of 74 patients with EML4-ALK translocation (37 per arm), the required 58 progression events for the superiority test would be observed by 1.75 additional years of follow-up after accrual completion.

13.4 Patient Accrual

CALGB 30407 accrued approximately 50 patients per year or 4-5 patients per month. RTOG 0617 (phase III trial for stage III A/B NSCLC) accrued approximately 10 patients per month. With an increasing interest in molecular-guided lung cancer trials in NRG Oncology and the Alliance, and the endorsement from other cancer cooperative groups as indicated above, we expect to enroll 6 patients to the EGFR mutant cohort and 3 patients to the ALK translocation cohort to the study per month. The prevalence rates in North America are ~10% for EGFR mutation and ~5% for EML4-ALK translocation. Once the target accrual is met for each mutation type, a notice suspending accrual for that cohort will be issued.

We project that the accrual during the first 6 months will be negligible, in part due to the process of IRB approval and logistical arrangement for the mandatory screening of the relevant tumor biomarkers. After the initial 6 month period, the accrual will be monitored on a quarterly basis and reviewed semi-annually by the NRG Oncology Data Monitoring Committee (DMC). Despite

our confidence that accrual goals will be met, the low prevalence of patients with EGFR mutant and ALK translocation tumors warrants that we closely monitor accrual, and the projected accrual for both cohorts may be re-estimated during the study. The study Senior Statistician will re-evaluate the feasibility of trial completion, and make recommendations regarding corrective actions or closure to DMC accordingly. The trial will be considered for modification or closure due to poor accrual if any of the following conditions occur:

- zero patients have been randomized by quarter 4;
- ≤ 6 patients have been randomized to the EGFR mutation cohort or ≤ 3 patients have been randomized to the ALK cohort by quarter 6;
- ≤ 18 patients have been randomized to the EGFR mutation cohort or ≤ 9 patients have been randomized to the ALK cohort by quarter 8.

13.5 Statistical Design for Translational Research

The number of randomized patients with useable specimens for genomic sequencing will be determined, and reasons for unusable specimens will be documented. Due to the exploratory nature of the corrective sciences study, no formal power analysis is performed. Types and proportions of genomic alterations in evaluable paired specimens (tumor vs. germline DNA from peripheral blood) will be described. Fisher's exact tests (Agresti 2002) will be used to compare the response rates between patients with and without alterations. Kaplan-Meier curves and log rank tests will be used to characterize the differences in OS and PFS between alterations subgroups. In view of the fact that approximately 20 genomic alterations subgroups could be potentially detected and analyzed, p-values ≤ 0.0025 would be deemed statistically significant using the Bonferroni method (Dunn 1961) for multiple comparisons. Alteration-alteration and alteration-treatment interactions may be performed depending on the limitations of sample size/number of events using logistic regression for response rate and Cox proportional hazard models for OS and PFS. A detailed plan for any additional translational research investigations will be submitted as an amendment to the protocol for CTEP review prior to commencement of such studies.

13.6 Analysis Plan

13.6.1 Statistical Methods

For the primary analysis, ineligible patients or patients who withdrew before receiving any protocol treatment will be excluded. The primary endpoint is PFS, which is defined as the time from randomization to disease progression or death of any cause, whichever occurs first.

The primary endpoint is progression-free survival (PFS). A rigorous definition of PFS is provided in Section 11.4. Due to the limitations of PFS in solid tumors (Bhattacharya 2009), efforts will be made to minimize any potential bias introduced in assessment during study conduct, and appropriate sensitivity analyses (FDA 2007) may be conducted accordingly to assure the robustness of analysis results. Separate set of analysis will be conducted for each mutation type with comparison to the respective control arm.

For these time-to-event endpoints (PFS and OS), the product limit estimator developed by Kaplan and Meier (1958) will be used to characterize outcomes by treatment arm. From the product limit estimates, median PFS and OS and 12-month PFS and OS as well as their 95% confidence intervals will be estimated. Comparisons between arms will be conducted using a log rank test. Cox proportional hazards model will be used to estimate the hazard ratio and their 95% confidence intervals of Arm 2 relative to Arm 1 (EGFR cohort) or Arm 4 relative to Arm 3 (ALK cohort) with and without adjusting for stratification factors. As an exploratory analysis, the survival and PFS endpoints will be related to prognostic factors, such as treatment, tumor size, performance status, pulmonary dysfunction, age, and weight loss, using the Cox proportional hazards model or an appropriate alternative in the case of model assumption violations. A step-down procedure that consists of dropping the least significant covariates, one at a time, will be used to obtain a more parsimonious model. Other time to event endpoints, such as local-regional progression-free survival (LRPFS) and distant progression-free survival (DPFS) will be similarly analyzed. For these endpoints, appropriate methods for competing risks will be applied,

specifically cumulative incidence functions (Kalbfleisch 2002) for estimation of cumulative cause specific event probabilities with associated testing for differences (Gray 1988), and regression methods for cause-specific hazards (Kalbfleisch 1978) and subdistribution hazards underlying cumulative incidence functions (Fine 1999) may be applied accordingly for exploratory purposes. RPFS is defined as the time from randomization to local-regional progression or death, whichever occurs first, and DPFS is defined as the time from randomization to distant progression or death, whichever occurs first.

The proportion of patients who respond (completely or partially) to each treatment will be estimated as well as their 95% confidence intervals. Response rates will be tested using Fisher's exact test and using a logistic regression model (Agresti 2002) to incorporate other prognostic covariates. Similar analysis will be done for primary tumor control rate.

The type and grade of treatment-related toxicity associated with each treatment regimen will be summarized using frequency table methods.

The primary analysis will be based on local assessments of mutation status, which determines if a patient is eligible and can be randomized. The extent of agreement and cross-classification pattern will be evaluated between local assessment and central review for EGFR and ALK mutations.

13.6.2 Interim Analysis for Futility

An interim analysis for the futility hypothesis that the experimental arm is not effective as or unlikely to be more effective than the standard arm will be performed after half of the required events (44 for EGFR and 29 for ALK) has been reached. At the futility analysis, we will compare the distribution of the PFS of the experimental and the standard arm for each cohort. If the observed hazard ratio (experimental/standard) is greater than or equal to 1.0, then the corresponding cohort will be terminated early at the interim analysis for futility (i.e., the experimental arm will be considered ineffective in this disease population) and the results will be reported. If the observed hazard ratio of the experimental arm relative to the standard arm is less than 1.0, then the trial will continue to the full target accrual. Under reasonable assumptions, termination of the corresponding cohort for futility at the interim analysis using this rule is found to result in minimal loss of power (less than 2%) for the primary hypothesis test (Wieand 1994). If the observed hazard ratio (experimental/standard) is ≥ 1.0 , a decision about whether to terminate accrual to the specific marker cohort and release the results will be made after consultation with the NRG Oncology Data Monitoring Committee (DMC) and NCI/CTEP.

13.6.3 Toxicity Monitoring

Erlotinib has been used extensively in the treatment of NSCLC over the past 5 years. Even though crizotinib has been approved for use in the United States for patients with advanced NSCLC whose tumor cells harbor EML4-ALK translocation, available evidence indicates that it is well tolerated and severe therapy-related complications are quite low. In this study, patients enrolled to the experimental arm will be receiving either single agent erlotinib or crizotinib before chemoradiation. We do not feel that it is necessary to conduct weekly monitoring for toxicities.

13.6.4 Interim Analyses to Monitor Study Progress

Interim reports with statistical analyses are prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The reports contain:

- Patient accrual rate with 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 efficacy endpoints (PFS, OS, etc.). The NRG Oncology Data Monitoring Committee (DMC) will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community.

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.

13.7 Gender and Minorities

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	3	4	7
Not Hispanic or Latino	91	136	227
Ethnic Category: Total of all subjects	94	140	234
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	0	1	1
Asian	3	3	6
Black or African American	10	13	23
Native Hawaiian or other Pacific Islander	0	1	1
White	81	122	203
Racial Category: Total of all subjects	94	140	234

REFERENCES

- Agresti A. *Categorical Data Analysis*. Wiley; 2002.
- Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol*. 2005; 23(25):5883-91. Epub 2005 Aug 8.
- Bhattacharya, S., Fyfe, G., Gray, R. J., and Sargent, D. J. Role of sensitivity analyses in assessing progression-free survival in late-stage oncology trials. *J Clin Oncol*. 2009; 27, 5958-5964.
- Blackstock AW, Govindan R. Definitive chemoradiation for the treatment of locally advanced non small-cell lung cancer. *J Clin Oncol*. 2007;25:4146-52.
- Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol*. 2010;11:521-9.
- Choy H, MacRae R, Milas L. Basic concepts of chemotherapy and irradiation interaction. In: Halperin EC, Perez CA, Brady LW, Schmidt-Ullrich RK, eds. *Principles and practice of radiation oncology*. 4th ed. Baltimore: Lippincott Williams and Wilkins; 2004: 736-756.
- Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: Randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011 103(19):1452-60. Epub 2011 Sep 8. Erratum in: *J Natl Cancer Inst*. 2012; 104 (1):79.
- DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;373:1097-104.
- Dunn, O.J. Multiple comparisons among means. *J Am Stat Assoc*. 1961; 56, 52-64.
- Eberhard DA, Giaccone G, Johnson BE. Biomarkers of response to epidermal growth factor receptor inhibitors in Non-Small-Cell Lung Cancer Working Group: Standardization for use in the clinical trial setting. *J Clin Oncol*. 2008; 26: 983-94.
- FDA Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics. 2007 Accessed November 2011, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999; 94:496–509.
- Fong T, Morgensztern D, Govindan R. EGFR inhibitors as first-line therapy in advanced non-small cell lung cancer. *J Thorac Oncol*. 2008; 3: 303-10.
- Govindan R, Bogart J, Wang X, et al. Phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small cell lung cancer: CALGB 30407. *J Clin Oncol*. (Meeting Abstracts) 2009; 27: 7505.
- Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Statistics*. 1988; 16:1141-1143.

REFERENCES (Continued)

- Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: The Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol*. 2008.
- Heinzerling JH, Hughes RS, Govindan R, et al. A phase I study of pemetrexed plus carboplatin or cisplatin with concurrent chest radiation therapy (CRT) for patients with locally advanced non-small cell lung cancer (LANSCLC). *J Clin Oncol*. (Meeting Abstracts) 2009; 27: 7545.
- Kalbfleisch JD, Prentice RL, Peterson AV Jr, et al. Analysis of failure times in presence of competing risks. *Biometrika*. 1978; 34:541–554.
- Kalbeisch,JD, Prentice RL. *The Statistical Analysis of Failure Time Data*, 2nd Edition, 2002; New York: Wiley-Interscience.
- Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol*. 2008; 26: 2450-6.
- Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet*. 2008; 372:1809-18.
- Klein J, Moeschberger M. *Survival Analysis: Techniques for Censored and Truncated Data*. Springer; 2003.
- Kwak EL, Bang Y-J, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *NEJM*. 2010 Oct. 28;363(18):1693–1703
- Langer CJ, Wakelee H, Schiller J, et al. Cooperative group portfolio in locally advanced non-small-cell lung cancer: are we making progress? *Clin Lung Cancer*. 2008; 9:85-91.
- Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *NEJM*. 2009; 361: 947-57.
- Morgensztern D, Goodgame B, Baggstrom MQ, Gao F, Govindan R. The effect of FDG-PET on the stage distribution of non-small cell lung cancer. *J Thorac Oncol*. 2008; 3:135-9.
- Movsas B, Scott C, Langer C, et al. Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: radiation therapy oncology group trial 98-01. *J Clin Oncol*. 2005; 23(10): 2145-54.
- Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497-500.
- Ready N, Janne PA, Bogart J, et al. Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial. *J Thorac Oncol*. 2010; 5: 1382-90.
- Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. *NEJM*. 2005; 353: 1673-84.
- Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *NEJM*. 2006; 355: 2542-50.

REFERENCES (Continued)

- Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008; 26: 3543-51.
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *NEJM*. 2005; 353: 123-32.
- Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007; 448: 561-6.
- Spigel DR, Hainsworth JD, Yardley DA, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. *J Clin Oncol*. 2010; 28:43-8.
- Vokes EE, Senan S, Treat JA, Iscoe NA. PROCLAIM: A phase III study of pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III non-small-cell lung cancer of other than predominantly squamous cell histology. *Clin Lung Cancer*. 2009; 10: 193-8.
- Wheatley-Price P, Ding K, Seymour L, Clark GM, Shepherd FA. Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol*. 2008; 26: 2350-7.
- Wieand S, Schroeder G, O'Fallon JR. Stopping when the experimental regimen does not appear to help. *Stat Med*. 1994; 13(13-14):1453-8.

APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (6/26/15)

*See [Section 11.2](#) for details and exceptions

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days)
Institution's biomarker screening and documentation of mutation	X	
Mediastinal staging (by mediastinoscopy, mediastinotomy, EBUS-TBNS, EUS, or VATS)	X	
Tissue submission for retrospective central review of biomarker screening	42	
*Tumor measurements	42	
*History/Physical exam	45	
Performance status	14	
Whole body FDG-PET/CT	30	
*CT scan with contrast of the chest and upper abdomen to include liver and adrenals	30	
*MRI of brain with contrast or CT scan with contrast	30	
CBC/differential; ANC, platelets; hemoglobin	14	
Creatinine clearance	14	
AST/ALT, bilirubin	14	
Serum pregnancy (if applicable)	14	
Pulmonary consultation and pulmonary function testing		Recommended: 56
EKG and/or echo		Recommended: 56
Lung ventilation/perfusion scan +/- CT scan		Recommended: 56
*Nutritional assessment		Recommended: 56
†Tissue submission for banking	Recommended at pre-treatment	
†Serum, plasma, & whole blood submission for banking	Recommended at pre-treatment	

†For patients who consent to participate in this component of the study

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT (6/26/15)

*See [Section 11.2](#) for details and exceptions

Assessments	During Treatment	
	Arms 1 and 3: q3 weeks during erlotinib or crizotinib	All Arms: q3 weeks during chemoradiation
*History/Physical exam	X	X
Performance Status	X	X
*Tumor measurements by CT scan with contrast of chest & upper abdomen to include liver and adrenals	After 6 weeks of oral induction therapy and at the completion of oral induction therapy	Patients receiving paclitaxel and carboplatin: 4-6 weeks after completion of chemoradiation (see Section 11.2.2)
CBC, platelets, serum creatinine, bilirubin, AST/AST, alk phos	X	
CBC, platelets, serum creatinine, and bilirubin		Weekly for patients receiving paclitaxel and carboplatin
CBC, platelets, serum creatinine		Weeks 1, 2, 5, and 6 for patients receiving cisplatin and etoposide
Adverse event evaluation	Weekly; may be done over the phone by study nurse/CRA	Weekly

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP (6/26/15)

*See [Section 11.2](#) for details and exceptions

Assessments	Follow Up		
	At 1 month Post-Treatment	At 2 mos. Post-Treatment	q3 mos. x 2 yrs; q6 mos. x 3 years; then annually
*History/Physical exam			X
Performance Status			X
CT scan with contrast of the chest and upper abdomen to include liver and adrenals	4-6 weeks after completion of chemoradiation.		X
Adverse event evaluation	X	X*	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.

LUNG

Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor.
Tis	Carcinoma <i>in situ</i>
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: parietal (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodules in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

APPENDIX III (Continued)

AJCC STAGING SYSTEM

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

LUNG

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*

M1b Distant metastasis

* Most pleural (and pericardial effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element, and the patient should be classified as M0.

STAGE GROUPING

Occult Carcinoma	TX, N0, M0
Stage 0	Tis, N0, M0
Stage IA	T1a-b, N0, M0
Stage IB	T2a, N0, M0
Stage IIA	T2b, N0, M0 T1a-b, N1, M0 T2a, N1, M0
Stage IIB	T2b, N1, M0 T3, N0, M0
Stage IIIA	T1a-b, N2, M0 T2a-b, N2, M0 T3, N1-2, M0 T4, N0-1, M0
Stage IIIB	T1a-b, N3, M0 T2a-b, N3, M0 T3, N3, M0 T4, N2-3, M0
Stage IV	Any T, Any N, M1a-b

APPENDIX IV: BIOSPECIMEN COLLECTION (6/26/15)
FFPE Specimen Plug Kit Collection
Blood Collection Kit Instructions

Shipping Instructions:

Courier Address (FedEx, UPS, etc.): For Frozen and Trackable Central Review 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 Specimen Transmittal (ST) Form has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
 - Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
 - FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the blocks or slides shaking it is likely that they will break during shipping.
 - Slides, Blocks, or Plugs can be shipped ambient or with a cold pack during the warmer seasons. For required central review material should only be shipped by Courier to the Street Address (94115). **Do NOT ship on Dry Ice.**

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

- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

APPENDIX IV (Continued)

FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank – San Francisco. 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. **Site are to embed the punches before shipping and include an H&E slide of the new block. Label the new block with**

accession number and block id



Step 2-3: For sites that are unable to embed the punches:

Label the punch tool with the proper specimen ID and block id. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail 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.

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 – San Francisco 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 and include a return label.

Ship punch block with H&E or 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 e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

**Courier Address (FedEx, UPS, etc.): For Central Review and Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco**

2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-RTOG (7864) or e-mail: NRGBB@ucsf.edu

APPENDIX IV (Continued)

BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood (as specified by the protocol):

Kit contents: Note: Sites must provide their own blood draw tubes. If a site is unable to provide the blood draw tubes they must request the tubes be included when they request the kit.

- Twenty-one (21) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- 1 Styrofoam container (inner) and 1 Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

- Label as many 1ml cryovials (5 to 8) as necessary for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin 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 Form.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 8) labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

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

(B) Plasma (If requested): 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, time, and time point, and clearly mark cryovials "plasma".

Process:

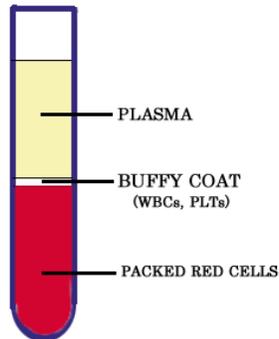
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
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.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.

6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

APPENDIX IV (Continued)

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

BLOOD COLLECTION KIT INSTRUCTIONS (continued)



(C) Whole Blood for DNA (if requested): 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/time, and time point, 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".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

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

Freezing and Storage:

- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- Store at -80°C (-70°C to -90°C) until ready to ship.
If a -80°C Freezer is not available,
 - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

OR:

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

OR:

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

- Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

APPENDIX IV (Continued)

BLOOD COLLECTION KIT INSTRUCTIONS (continued)

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). **Add padding to avoid the dry ice from 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 collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415) 476-7864.**

Shipping Address:

**Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu**