A Randomized Phase III Trial for Surgically Resected Early Stage Non-Small Cell Lung Cancer: Crizotinib versus Observation for Patients with Tumors Harboring the Anaplastic Lymphoma Kinase (ALK) Fusion Protein

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STUDY PARTICIPANTS

US Sites Only
ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG

ACTIVATION DATE

April 4, 2017
Addendum #1 – Incorporated Prior to Activation
Update #1 – Incorporated Prior to Activation
Addendum #2 – 9/14
Addendum #3 – 4/15
Addendum #4 – 7/15
Addendum #5 – 1/16
Addendum #6 – 5/16
Addendum #7 – 2/17
Update #2 – 6/17
Addendum #8 – 6/17

Agents	IND#	NSC#	Supply	IND Holder
Crizotinib	120790	NSC 749005	Pfizer	ECOG-ACRIN

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866-651-CTSU Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website 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.		
For clinical questions (i.e. patient eligibility or treatment-related): Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or data submission): Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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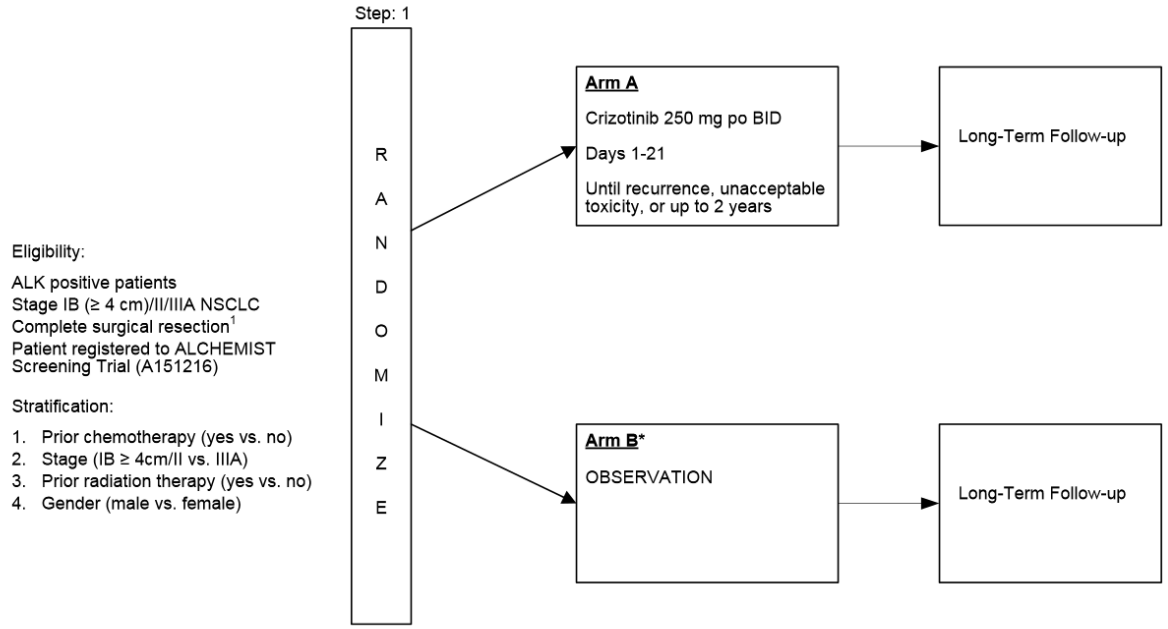
Schema



Accrual Goal: 378 patients
Cycle= 3 weeks (21 days)

1. Patients must have completed any prior surgery 4 or more weeks prior to randomization and be adequately recovered at time of randomization. Maximum time between surgery and randomization is 3 months if no adjuvant chemotherapy was administered, 8 months if adjuvant chemotherapy was administered, and 10 months if adjuvant chemotherapy and radiation therapy were administered.

*Prior to activation of Addendum 8, Arm B patients were receiving placebo

1. Introduction

1.1 Early stage NSCLC

Approximately 175,000 cases of non-small cell lung cancer (NSCLC) are diagnosed each year in the United States[1]. Of these, nearly a third of the patients have early stage disease that is amenable to surgical resection. Surgical resection alone results in cure rates of approximately 25 to 70% for patients with stages I to IIIA NSCLC[2]. The majority of recurrences occur at distant sites suggesting that micrometastasis is an early event. In fact, pilot studies have documented the presence of micrometastatic cells in the bone marrow of patients with early stage disease[3]. Therefore, eradication of micrometastatic disease is an important objective following surgical resection for patients with early stage NSCLC.

Adjuvant chemotherapy with cisplatin-based regimens has resulted in modest improvements in 5-year survival[4]. Several randomized studies in patients with stages IB to IIIA NSCLC have documented an absolute improvement in the 5-year survival rate by 4-15%[5-7]. Based on these results, adjuvant chemotherapy has become the standard of care for patients with lymph node positive disease or with primary tumor of > 4 cm size. Three to four cycles of cisplatin-based chemotherapy are administered in the post-operative setting for patients with a good performance status and life expectancy. In patients with stage IA disease or those with IB (tumor < 4 cm), there is no clear benefit with adjuvant chemotherapy, and the former group may actually be harmed[4]. It is clear that novel therapeutic modalities are required to individualize therapies and improve outcome for patients with early stage NSCLC. Ongoing studies are evaluating treatment selection based on ERCC1 (determinant of sensitivity to platinum), EGFR status (sensitivity to EGFR tyrosine kinase inhibitors) and thymidilate synthetase (sensitivity to pemetrexed). The Eastern Cooperative Group is evaluating the addition of bevacizumab (an inhibitor of vascular endothelial growth factor) to standard chemotherapy in patients with early stage NSCLC. Accrual to this study is ongoing with nearly 1200 patients enrolled (estimated sample size 1500).

1.2 EML4-ALK rearrangement

EML4-ALK fusion protein is a dominant oncogenic protein that is present in approximately 4 to 5% of all cases of NSCLC[8]. Patients with this fusion protein experience robust responses to inhibition of the Anaplastic Lymphoma Kinase (ALK) tyrosine kinase, similar to those seen with epidermal growth factor receptor (EGFR) inhibitors in those with an activating mutation in exons 19 or 21[9]. In addition to EML4, several other fusion partners have also been described for Anaplastic Lymphoma Kinase (ALK), although the functional differences based on the type of fusion protein are not known. Based on these exciting observations, screening of NSCLC tumors for ALK is now entering the routine clinical practice. ALK rearrangement is associated with clinical characteristics such as adenocarcinoma histology, signet ring features, and in never or light smokers[10]. Several methods are currently being studied for detection of the ALK fusion protein including immunohistochemistry (IHC) for protein expression, fluorescence in situ hybridization (FISH) assay and RT-PCR[20,21]. The FISH assay

is currently considered the 'standard' procedure for detection of ALK fusion protein.

1.3 Crizotinib

Crizotinib is a potent and selective ATP-competitive inhibitor of the MET, ALK, ROS1, and RON tyrosine kinases[11]. It was approved by the FDA for the treatment of ALK positive patients with advanced NSCLC on August 25, 2011. The efficacy of crizotinib has been studied in two large non-randomized clinical trials for patients with ALK positive, advanced stage NSCLC[12,13]. In a study by Camidge and colleagues, 119 patients with ALK positive NSCLC received crizotinib at a dose of 250 mg twice daily[13]. These patients had progressed on standard chemotherapy regimens prior to study entry. The response rate was 61% and the clinical benefit rate was nearly 90% for this molecularly selected sub-group of patients. Furthermore, the median progression-free survival was 10 months and the median survival has not been reached. The preliminary results of another phase II study by Crino and colleagues also documented robust response rates and disease control rate with crizotinib[12]. Crizotinib is now being studied in randomized clinical trials for patients with advanced stage NSCLC with ALK positive disease. Crizotinib is associated with a favorable tolerability profile. From the ongoing studies, it is clear that crizotinib can be administered for extended length of time, with some patients receiving the drug for over 3 years.

The efficacy of crizotinib in advanced stage NSCLC has been reported in two phase II clinical trials. In a study by Kwak and colleagues, 82 patients with advanced NSCLC were treated with crizotinib at a dose of 250 mg BID[9]. The majority of patients had progressive disease following prior platinum-based chemotherapy with a median of 2 prior regimens. The objective response rate was 57% and the 6-month progression-free survival rate was 72%. The median PFS and OS had not been reached at the time of this publication. Recently, Camidge and colleagues updated the results of this study[13]. This report included a total of 119 patients treated with crizotinib. The response rate was 61% with a median PFS of 10 months. The 1- and 2-year survival rates were 74% and 54% respectively and the median survival had not been reached. In another phase II study, Crino and colleagues treated 133 patients with ALK positive advanced NSCLC with crizotinib (250 mg BID)[13]. They reported a response rate of 51% and a clinical benefit rate of 90%. The disease control rate at 12 weeks was 74%. In addition, there were clinically meaningful improvements in symptoms such as cough, pain, dyspnea and fatigue. This study is ongoing with a planned sample size of 400 patients. In these studies median duration of response was 48 weeks.

In both of these studies, crizotinib was tolerated well with minimal grade > 2 toxicity. Fatigue and transaminitis were the only grade 3 toxicities reported in the study by Crino et al. Visual symptoms have been noted in approximately 40-57% of the patients and were grade 1 in 98% of the patients. The visual symptoms have been described as trails of light following objects moving relative to the observer, particularly during changes in ambient lighting from dark to light[9]. This often improves with continued therapy and is not associated with abnormalities on detailed ophthalmic evaluation. Other grade 1/2 toxicities include nausea, vomiting and diarrhea. Rare cases of pneumonitis have been reported with crizotinib, but the risk factors associated with this have not been clearly defined. Taken together, crizotinib has a very good tolerability profile and has been used

for extended lengths of time. The longest administered duration of therapy with crizotinib to date is approximately 3 years.

Results from the phase III PROFILE 1007 clinical trial were presented at the European Society for Medical Oncology (ESMO) 2012 Congress. In this study, 347 patients with previously treated ALK-positive advanced NSCLC were randomized to crizotinib or chemotherapy (pemetrexed or docetaxel). Crizotinib prolonged progression-free survival to a median of 7.7 months compared to 3.0 months among those patients treated with chemotherapy (HR 0.49; 95% CI 0.37-0.64; $P < 0.0001$). Overall response rate was significantly higher with crizotinib (65% versus 20%; $P < 0.0001$).

1.4 ALK-positive early stage NSCLC

There is now increasing knowledge regarding the natural history of ALK positive NSCLC. Shaw and colleagues reported recently that for ALK positive patients with metastatic NSCLC, the response to EGFR tyrosine kinase inhibitors was minimal, but the outcomes with chemotherapy were comparable to that in wild-type EGFR patients[10]. In addition, in a non-randomized cohort of patients, the outcome of ALK positive patients was considerably better with crizotinib therapy compared to those who did not receive it[14]. The prognosis of patients with early stage, ALK positive patients also appears to be sub-optimal compared to those without this genotype. In a cohort of approximately 200 patients with resected NSCLC, the presence of ALK fusion protein was associated with an adverse outcome[15]. The hazard ratio for overall survival was 2.3 with ALK positive disease compared to those without the fusion protein. Consequently, the use of crizotinib in patients with ALK positive NSCLC following surgical resection is a potential therapeutic option to improve the outcome. Therefore, we propose this randomized phase III study to compare crizotinib to placebo in patients with resected early stage NSCLC.

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As of Addendum #8, the placebo component will be dropped from this study and patients will be randomized between crizotinib and observation.

1.5 Rationale for the current study

Adjuvant chemotherapy has become a new standard of care for patients with early stage NSCLC. The present standard is to administer cisplatin-based chemotherapy for 3 to 4 cycles for patients with node positive disease or a primary tumor ≥ 4 cm in size. Cisplatin-based chemotherapy is associated with a 5-15% absolute improvement in 5-year survival rate for patients with stages IB, II and III NSCLC. Despite these advances, there is a clear need to improve methods to eradicate micrometastatic disease for patients with early stage NSCLC, since the survival rates continue to be less than 50% at 5 years for stages II and III disease. Ongoing studies are evaluating several novel strategies to improve outcomes for early stage NSCLC. A European study is evaluating the role of using ERCC1 as a biomarker to identify a platinum-sensitive subgroup of patients. The ECOG-ACRIN Cancer Research Group is conducting a phase III study to evaluate the efficacy of bevacizumab in combination with adjuvant chemotherapy for early stage NSCLC. Another phase III study with erlotinib following adjuvant chemotherapy has completed accrual and the results are eagerly awaited.

The molecular characterization of NSCLC in general, and adenocarcinoma in particular, has revealed several novel targets for therapy[16]. For patients with ALK positive NSCLC, crizotinib is an effective option in the metastatic disease as evidenced by a robust response rate, PFS and 1-year survival rate (74%). As a result, crizotinib has now become the preferred treatment option for this molecular sub-group of NSCLC patients. Given these exciting results, it will be important to evaluate the role of crizotinib in patients with earlier stages of NSCLC. The data available at present suggests that the overall survival for patients with ALK positive NSCLC is inferior compared to ALK negative patients following surgical resection[17]. Therefore, the use of crizotinib could result in an improvement in disease-free survival and overall survival for early stage ALK positive NSCLC. This question is particularly relevant since we anticipate that a higher proportion of NSCLC patients are likely to be diagnosed with earlier stages of the disease following the recent results of the National Lung Screening Trial (NLST) study (early detection of lung cancer with CT screening).

The importance of conducting a prospective study to evaluate the role of crizotinib in early stage NSCLC is underscored by the results of the NCIC-BR19 study that evaluated the role of gefitinib in a similar setting. This phase III study randomized patients with stage I NSCLC to gefitinib or placebo following surgical resection[18]. Unfortunately, the study was closed early due to lack of survival benefit with gefitinib in metastatic NSCLC (ISEL study)[19]. As a result, the median duration of exposure to gefitinib was low at approximately 5 months. For the patients treated on the study, there was an inferior outcome with gefitinib. Furthermore, even in patients with an *EGFR* mutated tumor, the hazard ratio was 1.2 with gefitinib. These results argue against the routine use of EGFR inhibitors in adjuvant therapy setting for *EGFR* mutated tumors pending further studies (ALLIANCE A081105).

For these reasons, conducting a prospective clinical trial to evaluate the role of crizotinib in the adjuvant therapy setting represents an important clinical need. In addition, the availability of tumor tissue in the surgical specimens in the adjuvant setting provides the opportunity to conduct biomarker studies to specifically address the prognostic and predictive impact of individual ALK fusion partners, and also identify other potential biomarkers of prognosis.

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1.6 ALCHEMIST-SCREEN (ALLIANCE A151216) study

E4512 is part of the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST), a clinical trial platform conceived to facilitate the development of adjuvant targeted therapies for genotype-defined lung cancer populations. In its initial phase, ALCHEMIST will consist of three integrated protocols:

- **ALCHEMIST-EGFR (A081105)** is a randomized trial of adjuvant erlotinib versus observation in EGFR-mutant lung adenocarcinoma.

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- **ALCHEMIST-ALK (E4512)** is a randomized trial of adjuvant Crizotinib versus observation in ALK--mutant lung adenocarcinoma.
- **ALCHEMIST – ANVIL (EA5142)** is a randomized trial of adjuvant nivolumab in patients not otherwise eligible for A081105 or E4512.

FW P1 **ALCHEMIST-SCREEN (A151216)** is the platform trial to which all subjects must consent, which will perform central genotyping of EGFR and ALK, will collect additional tissue for advanced genomic analysis, and will clinically follow subjects not participating in the above trials.

All patients participating in E4512 must be registered to ALCHEMIST-SCREEN (ALLIANCE A151216) and pre-trial diagnostic tumor specimens must be submitted for ALK fusion status assessments. Prior to randomization on E4512, ALK fusion status may have been determined either by local CLIA certified laboratory or centrally via ALCHEMIST-SCREEN trial (A151216). Patients who are randomized based on a locally determined ALK fusion status must be registered to ALCHEMIST-SCREEN (A151216) within four weeks of randomization to treatment on E4512.

ALCHEMIST-SCREEN (A151216) study will accrue patients that are potentially ALCHEMIST-SCREEN (A151216) study will accrue patients that are potentially eligible for the Intergroup adjuvant studies and perform central EGFR and ALK genotyping using a central reference laboratory certified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Patients may either present prior to surgery with resectable NSCLC, may present following complete resection (before or after adjuvant chemotherapy). Eligibility is limited to those with NSCLC of a non-squamous histological subtype and those with adequate performance status and organ function for future trial eligibility. All subjects must submit tissue for central EGFR and ALK genotyping, as well as additional tissue for advanced genomics at the CCG. Subjects may have had local genotyping done prior to randomization, however if the results show no targetable EGFR or ALK alterations (or if it shows a KRAS mutation) the patient will be eligible for this screening protocol given the primary aim is to facilitate accrual to the adjuvant studies. All subjects will provide peripheral blood for matched normal DNA.

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2. Objectives

2.1 Primary objective:

To evaluate whether adjuvant therapy with crizotinib will result in improved overall survival (OS) for patients with stage IB ≥ 4cm, II and IIIA, ALK-positive NSCLC following surgical resection.

2.2 Secondary objectives:

2.2.1 To evaluate and compare disease-free survival (DFS) associated with crizotinib

2.2.2 To evaluate the safety profile of crizotinib when given in the adjuvant therapy setting

2.2.3 To collect tumor tissue and blood specimens for future research.

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3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

NOTE: **The 7th edition of the AJCC Cancer Staging Manual will be used for the disease stage criteria for E4512.**

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3.1 Randomization Eligibility Criteria

_____ 3.1.1 Age ≥ 18 years.

_____ 3.1.2 Patients must have undergone complete surgical resection of their stage IB (≥ 4 cm), II, or non-squamous IIIA NSCLC per AJCC 7th edition and have had negative margins. N3 disease is not allowed.

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_____ 3.1.3 Baseline Chest CT with or without contrast must be performed within 6 months (180 days) prior to randomization to ensure no evidence of disease. If clinically indicated additional imaging studies must be performed to rule out metastatic disease.

_____ 3.1.4 ECOG performance status 0 or 1 (Refer to Appendix IV).

_____ 3.1.5 Patients must be registered to the ALCHEMIST-SCREEN (ALLIANCE A151216) trial prior to randomization.

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_____ 3.1.6 Positive for translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as defined by a CLIA-approved test including: (1) translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as determined by the Vysis Break Point FISH assay; (2) ALK protein expression by immunohistochemistry (IHC); or (3) ALK rearrangement identified by Next Generation (NextGen) sequencing. This must have been performed:

3.1.6.1 By a local CLIA certified laboratory: Report must indicate the results as well as the CLIA number of the laboratory which performed the assay. Tissue must be available for submission for central, retrospective confirmation of the

ALK fusion status via ALCHEMIST-SCREEN (ALLIANCE A151216).

OR

3.1.6.2 Patient registered to and the ALK fusion status performed centrally on the ALCHEMIST-SCREEN (ALLIANCE A151216).

_____ 3.1.7 Women must not be pregnant or breast-feeding because, based on the mechanism of action, crizotinib may cause fetal harm when administered during pregnancy. In animal studies, teratogenicity was not evident, but embryotoxic and fetotoxic effects were noted in rats at crizotinib exposures similar to and above those observed in humans at the recommended clinical dose.

_____ 3.1.8 All females of childbearing potential must have a blood or urine pregnancy test within 72 hours prior to randomization to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of childbearing potential? _____ (Yes or No)

Date of blood or urine test: _____

_____ 3.1.9 Women of childbearing potential and sexually active males must be strongly advised to practice abstinence or use an accepted and effective method of contraception.

_____ 3.1.10 Patients must NOT have uncontrolled intercurrent illness including, but not limited to, serious ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

_____ 3.1.11 No known interstitial fibrosis or interstitial lung disease.

_____ 3.1.12 No prior treatment with crizotinib or another ALK inhibitor.

_____ 3.1.13 No ongoing cardiac dysrythmias of Grade ≥ 2 NCI CTCAE version 4.0, uncontrolled atrial fibrillation (any grade), or QTc interval > 470 msec.

_____ 3.1.14 No use of medications, herbals, or foods that are known potent CYP3A4 inhibitors or inducers, included but not limited to those outlined in Appendix V.

_____ 3.1.15 Patients must be adequately recovered from surgery at the time of randomization.

_____ 3.1.15.1 The minimum time requirement between date of surgery and randomization must be at least 4 weeks (28 days).

_____ 3.1.15.2 The maximum time requirement between surgery and randomization must be:

☐ 3 months (90 Days) if no adjuvant chemotherapy was administered

☐ 8 months (240 Days) if adjuvant chemotherapy was administered

☐ 10 months (300 Days) if adjuvant chemotherapy and radiation therapy were administered.

_____ 3.1.16 Patients must have completed any prior adjuvant chemotherapy or radiation therapy 2 or more weeks (6 or more weeks for mitomycin and nitrosoureas) prior to randomization and be adequately recovered at the time of randomization.

NOTE: Patients taking low dose Methotrexate for non-malignant conditions and other cytotoxic agents for non-malignant conditions are allowed to continue treatment while on study.

NOTE: Neo-adjuvant chemotherapy or radiation therapy for the resected lung cancer is not permitted.

_____ 3.1.17 Patients must have adequate organ function as defined by the following criteria within 2 weeks prior to randomization:

NOTE: It is strongly encouraged that these tests take place no more than one week prior to randomization to meet the 2 week requirement for randomization:

_____ 3.1.17.1 Serum Aspartate Transaminase (AST) and Serum Alanine Transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN)

AST: _____ Date of Test:_____

ALT:_____ Date of Test:_____

_____ 3.1.17.2 Total Serum Bilirubin ≤ 1.5 x ULN

Total Bilirubin:_____ Date of Test:_____

_____ 3.1.17.3 Absolute neutrophil count (ANC) ≥ 1500/mm^3

ANC:_____ Date of Test:_____

_____ 3.1.17.4 Platelets ≥ 30,000/mm^3

Platelet count:_____ Date of Test:_____

_____ 3.1.17.5 Hemoglobin ≥ 8.0 g/dL

Hemoglobin:_____ Date of Test:_____

_____ 3.1.17.6 Serum Creatinine ≤ 2 x ULN

Serum Creatinine:_____ Date of Test:_____

_____ 3.1.18 Prior to randomization patients with any non-hematologic toxicity from surgery, chemotherapy, or radiation must have recovered to Grade ≤ 1 with the exception of alopecia and the criteria outlined in Section 3.1.17.

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_____ 3.1.19 Patients must not have any history of locally advanced or metastatic cancer requiring systemic therapy within 5 years from randomization, with the exception of in-situ carcinomas and non-melanoma skin

cancer. Patients must have no previous primary lung cancer diagnosed concurrently or within the past 2 years.

_____ 3.1.20 Patients may not be receiving any other investigational agents while on study.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration and Randomization Procedures

CTEP Investigator Registration Procedures:

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account:

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' website.

Additional information can be found on the CTEP website 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>.

CTSU Registration Procedures:

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. 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.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E4512** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E4512**
- Click on the Site Registration Documents link

Requirements for E4512 site registration:

- **CTSU IRB Certification (for sites not participating via the NCI CIRB)**
- **CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)**

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
FAX: (215) 569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents:

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (Replaces HHS 310 Form).
   Or
   C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.

- Signature of IRB official

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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

Patient Enrollment:

Patients must not start protocol treatment prior to randomization on Step 1.

Treatment should start within five working days after randomization.

Patient registration can occur only after pre-treatment evaluation 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.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

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.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: 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 OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Randomization (Step 1)

Please note that all eligibility criteria in Section 3.1, including the determination of the ALK mutation status and registration to ALCHEMIST SCREEN (ALLIANCE A151216), must be met prior to randomization.

Please note that when a patient has been successfully randomized, the confirmation of registration will indicate that the patient is on arm X. The patient

will actually be randomized to arm A or B, but as this is a double blinded trial, that information cannot be displayed.

Treatment should begin within five working days after randomization to Step 1.

The following information will be requested for randomization:

4.1.1 Protocol Number

4.1.2 Investigator Identification

- 4.1.2.1 Institution and affiliate name
- 4.1.2.2 Investigator's name

4.1.3 Patient Identification

- 4.1.3.1 Patient's initials and chart number
- 4.1.3.2 Patient's Social Security number
- 4.1.3.3 Patient demographics
  - 4.1.3.3.1 Gender
  - 4.1.3.3.2 Birth date (mm/yyyy)
  - 4.1.3.3.3 Race
  - 4.1.3.3.4 Ethnicity
  - 4.1.3.3.5 Nine-digit ZIP code
  - 4.1.3.3.6 Method of payment
  - 4.1.3.3.7 Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.1.5 Stratification Factors

- 4.1.5.1 Prior chemotherapy (Yes vs. No)
- 4.1.5.2 Stage per AJCC 7th edition (IB ≥ 4cm / II vs. IIIA)
- 4.1.5.3 Prior radiation therapy (Yes or No)
- 4.1.5.4 Gender (Male vs. Female)

4.1.6 Additional Requirements

- 4.1.6.1 Patients must provide a signed and dated, written informed consent form.

  NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

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4.1.6.2 Patients must be registered to ALCHEMIST SCREEN (ALLIANCE A151216) prior to randomization. Tumor tissue must be submitted per ALCHEMIST SCREEN (ALLIANCE A151216):

- ☐ Prior to randomization if ALK status is to be determined for patient eligibility for E4512. Results of the positive ALK translocation or inversion must have been received by the site.

OR

- ☐ Within 4 weeks after randomization to E4512 if the ALK testing was performed by a local CLIA laboratory.

4.1.6.3 Biological samples are to be submitted as indicated in Section 10.

4.1.6.4 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. 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. 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 in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS 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 members' 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.

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4.2 Investigational Brochure and Safety Alerts:

Crizotinib is an INVESTIGATIONAL AGENT (IND# 120790). The Investigator Drug Brochure (IDB) for, Crizotinib is available for download from the E4512 Study Specific Tools section of the ECOG webpage. The IDB provides relevant and current scientific information about the investigational product. The IDB should be submitted to your IRB/EC according to GCP regulations. The IDB and any correspondence to the Institutional Review Board (IRB)/Ethics Committee (EC) should be kept in the E4512 regulatory files.

Should any SAE report on this study qualify as a safety alert report requiring expedited reporting, the SAE report will be sent by the respective pharmaceutical company to regulatory authorities globally (including the FDA) and ECOG-ACRIN. If applicable, ECOG-ACRIN will disseminate these safety alert reports to all ECOG-ACRIN investigators in the bimonthly group mailings. These reports should be forwarded to your IRB/EC within 90 days of receipt for review. Reporting instructions are provided with each safety alert. These safety alerts and any correspondence to your IRB/EC should be maintained in your E4512 study files.

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4.3 Unblinding of Patients Effective with Addendum #8

Once Addendum #8 has been posted on the ECOG-ACRIN and CTSU websites, site will unblind any patients that have previously enrolled to E4512. Sites may obtain unblinding information from the link provided in the activation memo of Addendum #8. Additionally, the unblinded treatment assignment can be obtained by calling a member of the ECOG-ACRIN Operations Office – Boston drug team at (857) 504-2900 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., “E4512”), the patient ID number (e.g., “44444”), and the patient initials (e.g., “FL”) to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment. Once you have obtained the patient’s treatment assignment, patients should be contacted with the information either by site contact or by using the “E4512 Addendum #8 Patient Letter” that can be found on the ECOG-ACRIN and CTSU websites.

Patients receiving placebo will continue to follow up per Section 5.1.2. Patients randomized to blinded crizotinib will continue to receive open label crizotinib.

4.4 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E4512 Forms Completion Guidelines. Document the reason for not starting protocol treatment on the Off Treatment

form, and report the date and type of the first non-protocol treatment that the patient receives.

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5. Treatment Plan

In order to be eligible for this trial, all patients must have undergone complete resection of the cancer prior to enrollment. Accepted types of resection (with negative margins) will consist of lobectomy, sleeve lobectomy, bi-lobectomy, pneumonectomy, intrapericardial pneumonectomy, wedge resection or segmentectomy. Adjuvant chemotherapy and post-operative radiation therapy are permitted as indicated prior to study enrollment

5.1 Administration Schedule

Cycle = 3 weeks (21 days)

Crizotinib/placebo will be administered orally twice a day at 250 mg at approximately the same times each day on a continuous daily dosing schedule, i.e. no break in dosing. Doses should be taken 12 hours apart. The dose may be taken with or without food. Taking the medicine with food may reduce nausea. Capsules should be swallowed whole. Patients should be instructed that if they vomit anytime after taking a dose, then they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. See Appendix III for the Patient Capsule Calendar for Crizotinib/Placebo.

NOTE: No use of medications, herbals, or foods that are known potent CYP3A4 inhibitors or inducers, included but not limited to those outlined in Appendix V.

NOTE: There are two different capsule sizes (200 mg – for dose modifications or 250 mg).

NOTE: Doses should be taken 12 hours apart. Taking the medicine with food may reduce nausea.

5.1.1 ARM A

Crizotinib 250 mg po BID, days 1-21

Repeat cycles every 21 days

Maximum duration of treatment is 2 years

Effective Addendum #8: Patients currently randomized to ARM A will continue to receive crizotinib open-label.

5.1.2 ARM B (Placebo discontinued effective Addendum #8)

Placebo po BID, days 1-21

Repeat cycles every 21 days

Maximum duration of treatment is 2 years

Effective Addendum #8: Patients will be unblinded per Section 4.3 and will proceed directly to follow-up.

5.1.3 Effective Addendum #8

Patients randomized to ARM A will receive crizotinib open-label. Patients randomized to ARM B will be followed by observation.

5.1.3.1 ARM A – Crizotinib (Active Addendum #8)

Crizotinib 250 mg po BID, days 1-21

Repeat cycles every 21 days

Maximum duration of treatment is 2 years

5.1.3.2 ARM B – Observation (Active Addendum #8)

Patients randomized to observation will be followed serially with CT imaging as outlined in Section 7.3.

5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (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 product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment.
Unlikely	The AE is ***doubtfully related*** to treatment.
Possible	The AE ***may be related*** to treatment.
Probable	The AE is ***likely related*** to treatment.
Definite	The AE is ***clearly related*** to treatment.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a 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.

5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of Reporting Requirements

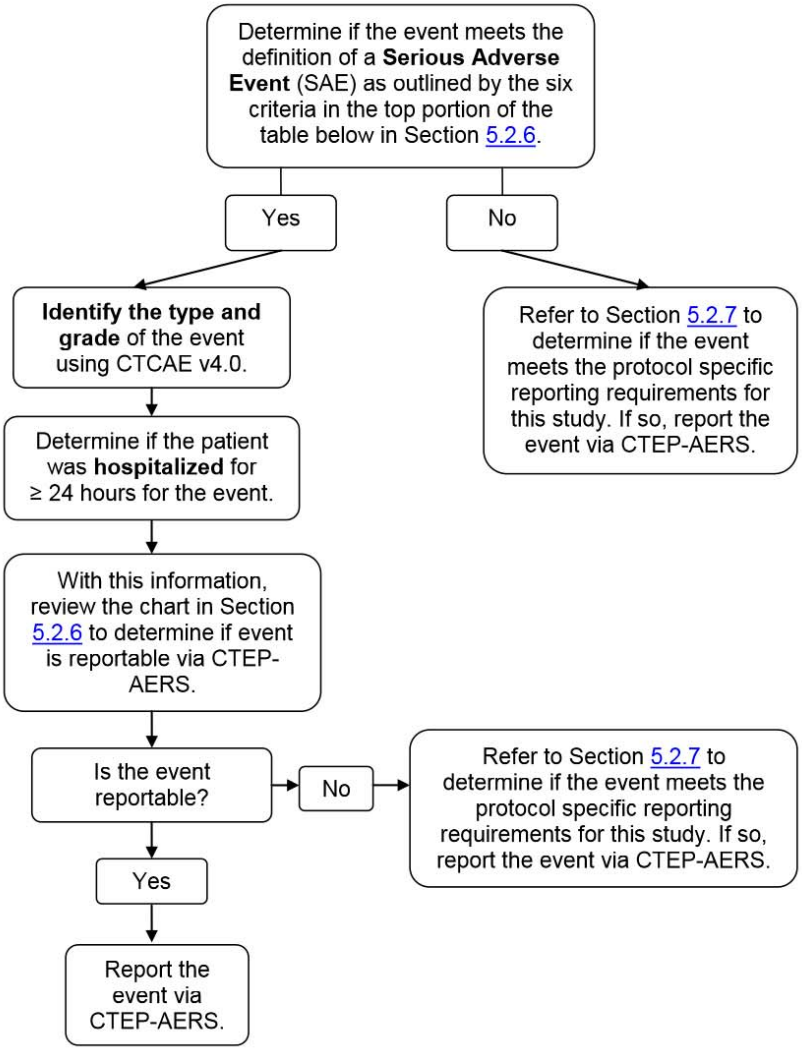
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E4512 and outline the specific expedited adverse event reporting requirements for study E4512.

5.2.5 Steps to determine if an adverse event is to be reported in an expedited manner

5.2.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.6, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

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

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

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

5.2.6 Expedited Reporting Requirements for Arm A (Crizotinib Arm) on protocol E4512

Investigational Agents: Crizotinib

Commercial Agents: None

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

5.2.7 Additional instructions, requirements and exceptions for protocol E4512

Additional Instructions:

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

E4512 specific expedited reporting requirements:

☐ **Pregnancy**

Pregnancies and suspected pregnancies (including a positive/inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on Crizotinib/Placebo, or within 28 days of the subject's last dose of Crizotinib/Placebo, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS** within 24 hours of the Investigator's **knowledge.** Please refer to Appendix VI for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

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E4512 specific expedited reporting exceptions:

☐ There are no SAE expedited reporting requirements for patients on Arm B (observation)

For patient previously enrolled on Arm X of this protocol: Any event that occurred *while patient was still on blinded treatment* that meets the SAE definition and reporting requirements outlined in Section 5.2.6 must be reported via CTEP-AdEERS regardless of whether the patient was receiving Crizotinib or the placebo.

5.2.8 Other recipients of adverse event reports and supplemental data

ECOG-ACRIN will provide CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

The drug supporter is obliged to forward reported AEs to the FDA. A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form within 14 days in Medidata Rave.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form within 14 days in Medidata Rave.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     - Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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5.3 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. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). Frequent is provided based on 2058 patients. Below is the CAEPR for Crizotinib (PF-02341066)

Version 2.1, March 4, 2016[1]

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 4.0 Term) [n= 2058]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
	Sinus bradycardia	
EYE DISORDERS		
Eye disorders - Other (vision disorders)[2]		
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
Constipation		
Diarrhea		
	Dyspepsia	
	Mucositis oral	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema face		
Edema limbs		
Fatigue		
General disorders and administration site conditions - Other (generalized edema)		
Localized edema		
INFECTIONS AND INFESTATIONS		
	Upper respiratory infection	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
		Blood bilirubin increased
	Creatinine increased	
		Electrocardiogram QT corrected interval prolonged
	Lymphocyte count decreased	
Neutrophil count decreased		
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Dysgeusia	
	Headache	
	Nervous system disorders - Other (neuropathy)[3]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Periorbital edema		
	Rash[4]	

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

[2] Vision 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.

[3] Neuropathy 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.

[4] Treatment-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; Heart failure; Myocarditis; Pericardial effusion; Supraventricular tachycardia

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

GASTROINTESTINAL DISORDERS - Colitis; Colonic perforation; Dysphagia; Esophageal ulcer; Esophagitis; 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

HEPATOBILIARY DISORDERS - Hepatic failure; 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 (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; Syncope

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.

5.4 Dose Modifications Possibly Related to Study Drug

If toxicity occurs **related to study drug**, the dose of crizotinib may be adjusted as indicated in the Table below. Intrapatient dose reduction by 1 and if needed, 2 dose level(s) will be allowed depending on the type and severity of toxicity encountered

- Dose Level -1 is 200 mg BID
- Dose Level -2 is 250 mg daily

Patients requiring more than 2 dose reductions due to treatment-related toxicity will be discontinued from protocol treatment.

If toxicities don't resolve to Grade ≤1 or baseline within 42 days, discontinue all protocol therapy.

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (version 4.0).

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALT or AST elevation with Grade ≤ 1 total bilirubin	Continue at the same dose level.	Continue at the same dose level.	Withhold until recovery to Grade ≤ 1 or baseline, then resume at 200 mg twice daily[a]	Withhold until recovery to Grade ≤ 1 or baseline, then resume at 200 mg twice daily[a]
ALT or AST elevation with concurrent Grade 2, 3, or 4 total bilirubin elevation (in the absence of cholestasis or hemolysis)	Continue at the same dose level.	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat
Pneumonitis[b]	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat
Left ventricular systolic dysfunction	Continue at the same dose level	Continue at the same dose level	Withhold until recovery to Grade ≤ 1 or baseline, then resume at 200 mg twice daily[a]	Discontinue treatment and do not retreat
Prolonged QTc	Continue at the same dose level	Assess electrolytes and concomitant medications. Correct any electrolyte or magnesium abnormalities	Withhold until recovery to Grade ≤1, then resume at 200 mg twice daily. Assess electrolytes and concomitant medications. Correct any electrolyte or magnesium abnormalities	Discontinue treatment and do not retreat
Visual disturbance	Continue at the same dose level.	Continue at the same dose level.	Withhold treatment until recovery. Resume treatment by reducing the dose to 200 mg BID	Discontinue treatment and do not retreat.
Non-hematologic General	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose or reduce the dose by 1 level at the discretion of the	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or

			investigator*.	discontinue at the discretion of the investigator*.
Hematologic (excluding lymphopenia**)	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤ 2, or has returned to baseline, then resume treatment at the same dose level**.	Withhold dose until toxicity is grade ≤ 2, or has returned to baseline, then reduce the dose by 1 level and resume treatment**.

[a] In case of recurrence, withhold until recovery to Grade ≤ 1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.

[b] Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect.

* Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification.

** Patients who develop Grade 3 or 4 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption.

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.2 Supportive care should include the use of antiemetic medications, of which ondansetron and prochlorperazine were the most commonly used in clinical trials. Prophylactic antiemetics may be used at the discretion of the treating physician.

5.5.3 Patients may receive prophylaxis of treatment-induced diarrhea. The specifics of the prophylactic regimen are at the discretion of the treating physician.

5.5.4 Patients should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study.

5.5.5 No use of medications, herbals, or foods that are known potent CYP3A4 inhibitors or inducers, included but not limited to those outlined in Appendix V.

5.5.6 The use of any non-prescription medications including analgesics should be discussed with the treating physician. Acetaminophen, if administered, should be limited to less than 2 grams per day.

5.6 Duration of Therapy

Patients randomized to crizotinib will receive protocol therapy for up to 2 years from Step 1 randomization unless:

- FO 69 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E4512 Forms Completion Guidelines.
- FO 67 Patient withdraws consent.
- FO 68 Patient shows evidence of recurrent NSCLC.

- A second primary develops (including a second lung primary), but not including squamous or basal cell carcinoma of the skin, or in situ of the cervix.

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- Unacceptable toxicity requiring discontinuation of treatment. Refer to Section 5.4.
- Need for treatment delay for more than 6 weeks (42 days) due to lack of toleration
- Global deterioration of health-related symptoms
- Protocol non-compliance
- Pregnancy

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for recurrence, even if non-protocol therapy is initiated, and for survival for 10 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Overall Survival

Overall survival will be measured from the date of randomization to Step 1.

6.2 Disease-Free Survival (DFS)

Date of randomization to the date of first treatment failure (recurrence or death before recurrence).

6.3 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. **The same imaging modality must be used throughout the study to measure disease.**

6.3.1 CT and MRI

CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors, and those of the extremities require specific procedures.

6.3.2 Cytology and Histology

Cytologic and histologic techniques can be used to differentiate between complete and partial response in rare cases (e.g., after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required.

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7. Study Parameters

7.1 Therapeutic Parameters (Arm A – Crizotinib)

1. Prestudy CBC (with differential and platelet count) must be done ≤ 2 **weeks** before randomization.
2. Pre-study vital signs, physical exam and all required pre-study blood tests, as outlined in Section 3.1 must be done ≤ 2 **weeks** before randomization.
3. For Cycles 1 and 2, assessments must be performed prior to the start of each treatment cycle (every 3 weeks). For cycles 3 through 6, assessments will be performed every other cycle (every 6 weeks). Starting with Cycle 7 - Day 1, assessments will be performed every 4 cycles (every 12 weeks) until treatment completion or recurrence.

	Pre-study	Cycles 1 and 2[3]	Cycles 7, 11, 15, 19 and every 4 cycles thereafter on Day 1[3]	Post cycle 4, every other cycle on day 1[3]	Follow-up[6]
Medical history/concurrent meds	X	X	X	X	
Physical exam/performance status	X	X	X	X	
Toxicity assessment	X	X	X	X	X
Weight, blood pressure, heart rate	X	X	X	X	
Height	X				
EKG[10]	X				
Liver chemistries[1]	X	X	X	X	
Serum[2]	X	X	X	X	
CBC with differential[4]	X	X	X	X	
Serum or Urine Pregnancy Test[5]	X				
Capsule Count/Diary		X	X	X	
Imaging[8]	X			X[8]	X[7]
Smoking status survey	X				
Pathology and surgical reports	X				At recurrence[7]
ALK Fusion Status[9]	X				
Biological sample submissions			See Sections 7.3 and 10		

1. Liver Chemistries, including Tbili, ALT, AST, AlkPhos, Total protein, Albumin, must be performed every 2 weeks (+/- 1 week) for the first 2 months and day 1 of each cycle thereafter. Rev. 1/16
2. Serum Chemistries: Na, K, Cl, Ca, Ph, BUN, Cr. uric acid, Mg, LDH.

3. For Cycles 1 and 2, assessments must be performed prior to the start of each treatment cycle (every 3 weeks). For Cycles 3 through 6, assessments will be performed every other cycle (every 6 weeks) Starting with Cycle 7, Day 1, assessments will be performed every 4 cycles (every 12 weeks) until treatment completion or recurrence.
4. CBCs (with differential and platelet count) which include WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 72 hours prior to the start of the treatment cycle. For cycle 1, the test results used for registration are acceptable and there is no need to repeat the lab work on day 1 of the cycle 1 if the clinical condition of the patient is unchanged.
5. Serum or urine pregnancy test (women of childbearing potential) required within 72 hours prior to randomization. All women of childbearing potential must have a negative pregnancy test (sensitivity of at least 50 mIU/mL). The pregnancy test must be performed within 72 hours prior to registration. A serum or urine pregnancy test (women of childbearing potential) must also be performed when the patient goes off treatment.
6 Toxicity assessment should be done every 6 months (180 days) if patient is < 5 years from study entry, and every 12 months (365 days) if patient is 6-10 years from study entry. H&P and a chest CT with or without contrast must be performed every 6 months (180 days) if the patient is < 4 years from study entry. H&P and a low-dose non-contrast-enhanced chest CT must be performed every 12 months (365 days) if patient is 5-10 years from study entry.
7. It is strongly encouraged that disease recurrence be documented by biopsy. If there is a recurrence, it is also strongly encouraged that patients be fully restaged, including a CT scan of the thorax and abdomen, imaging (preferably MRI, but CT is acceptable) of the brain and a radionuclide bone scan or positron emission tomography (PET) scan. If a biopsy is performed, molecular profiling is strongly encouraged (in particular, ALK gene sequencing to evaluate for secondary mutations).
   NOTE: From consenting patients, samples of the biopsy tissue are to be submitted as requested on ALCHEMIST-SCREEN (ALLIANCE A151216) and for E4512 as outlined in Sections 7.3 and 10.
8. Baseline Chest CT with or without contrast must be performed within 6 months (180 days) prior to randomization. Once randomized, a chest CT with or without contrast must be performed every 6 months (180 days) if the patient is <4 years from study entry. A low-dose non-contrast-enhanced chest CT must be performed every 12 months (365 days) if patient is 5-10 years from study entry. For additional imaging guidelines refer to Section 6.0, Measurement of Effect.
9. Positive for translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as defined by a CLIA-approved test including: (1) translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as determined by the Vysis Break Point FISH assay and defined by an increase in the distance between 5' and 3' ALK probes or the loss of the 5' probe; (2) ALK protein expression by immunohistochemistry (IHC); or (3) ALK rearrangement identified by Next Generation (NextGen) sequencing. This must have been performed by a local CLIA certified laboratory or patient registered to and the ALK fusion status performed centrally on ALCHEMIST-SCREEN (ALLIANCE A151216). All patients must be registered to ALCHEMIST-SCREEN (ALLIANCE A151216) prior to randomization. For patients who enter E4512 based on local ALK status results, tissue must be submitted for central confirmation of ALK fusion status within 4 weeks following randomization on E4512.
10. EKG must be done at baseline within 28 days prior to randomization.

7.2 Study Assessments in Arm B (Observation) and Arm B following unblinding (effective Addendum #8)

	Pre-study[1]	Subsequent Follow-up[8]
Medical history/concurrent meds	X	X
Physical exam/performance status	X	X
Toxicity assessment	X	
Weight, blood pressure, heart rate	X	X
Height	X	
EKG	X	
Liver chemistries[1]	X	
Serum Chemistries[2]	X	
CBC with differential[3]	X	
Serum or Urine Pregnancy Test for women of child bearing potential	X	
Imaging[4]	X	
Pathology and surgical reports	X	At recurrence[5]
ALK Fusion Status[6]	X	
Biological sample submissions[7]	X	At recurrence

1. Liver Chemistries including: Tbili, ALT, AST, AlkPhos, Total protein, Albumin.
2. Serum Chemistries including: Na, K, Cl, Ca, Ph, BUN, Cr. uric acid, Mg, LDH.
3. CBCs (with differential and platelet count) which include WBC, ANC, Platelets, Hgb, and Hct
4. Baseline Chest CT with or without contrast must be performed within 6 months (180 days) prior to randomization. Once randomized, a chest CT with or without contrast must be performed every 6 months (180 days) if the patient is < 4 years from study entry. A low-dose non-contrast-enhanced chest CT must be performed every 12 months (365 days) if patient is 5-10 years from study entry. For additional imaging guidelines refer to Section 6, Measurement of Effect.
5. It is strongly encouraged that disease recurrence be documented by biopsy. If there is a recurrence, it is also strongly encouraged that patients be fully restaged, including a CT scan of the thorax and abdomen, imaging (preferably MRI, but CT is acceptable) of the brain and a radionuclide

bone scan or positron emission tomography (PET) scan. If a biopsy is performed, molecular profiling is strongly encouraged (in particular, ALK gene sequencing to evaluate for secondary mutations).

NOTE: From consenting patients, samples of the biopsy tissue are to be submitted as requested on ALCHEMIST-SCREEN (ALLIANCE A151216) and for E4512 as outlined in Sections 7.3 and 10.

6. Positive for translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as defined by a CLIA-approved test including: (1) translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as determined by FISH; (2) ALK protein expression by immunohistochemistry (IHC); or (3) ALK rearrangement identified by Next Generation (NextGen) sequencing. This must have been performed by a local CLIA certified laboratory or patient registered to and the ALK fusion status performed centrally on ALCHEMIST-SCREEN (ALLIANCE A151216). All patients must be registered to ALCHEMIST-SCREEN (ALLIANCE A151216) prior to randomization. For patients who enter E4512 based on local ALK status results, tissue must be submitted for central confirmation of ALK fusion status within 4 weeks following randomization on E4512.
7. Specimen collection per protocol Section 7.3 and 10.
8. H&P and a chest CT with or without contrast must be performed every 6 months (180 days) if the patient is < 4 years from study entry. H&P and a low-dose non-contrast-enhanced chest CT must be performed every 12 months (365 days) if patient is 5-10 years from study entry.

7.3 Specimen Submissions

1. Time points indicate timing of collection of the samples.
2. All specimens submitted on **E4512** are to be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS). Samples submitted on ALCHEMIST-SCREEN (ALLIANCE A151216) are not tracked via ECOG-ACRIN STS.

	Prior to start of treatment	Cycle 5, prior to treatment	Progression or Recurrence	Submit To:
ALCHEMIST-SCREEN (ALLIANCE A151216) Submissions: Submission schedules and guidelines outlined within the ALCHEMIST-SCREEN (ALLIANCE A151216) protocol.				
All patients must be registered to ALCHEMIST-SCREEN (ALLIANCE A151216) prior to registration on E4512. Submission of diagnostic tumor tissue is mandatory. Refer to protocol A151216 for all submission instructions.				Per A151216
E4512 Submissions: Submission schedules and guidelines for E4512 are outlined in Section 10. From patients who answer "Yes" to "*My samples and related information may be kept in a Biobank for use in future health research.*"				
FFPE tumor tissue			X[2]	NCI CCG Biospecimen Core Resource
Serum from one red top tube	X	X	X	ECOG-ACRIN CBPF
Plasma from three (3) EDTA tubes	X	X	X	
Whole blood, ACD tube	X	X	X	

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1. [Deleted in Addendum #3] applies to the E4512 tissue submission in the table.
2. If available, submit tumor tissue at whichever occurs first. Tumor tissue is not requested at both time points.

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8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

NOTE: Under no circumstances can commercially supplied **crizotinib** be used or substituted for patient specific, the **crizotinib** supplied by Pfizer.

8.1 Crizotinib, NSC #749005/Placebo, IND #120790

8.1.1 Other Names

XALKORI®, PF 02341066

Chemical name: (R)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-pyridin-2-ylamine

8.1.2 Classification

Small molecule kinase inhibitor

8.1.3 Mode of Action

Crizotinib is a competitive inhibitor of the anaplastic lymphoma kinase (ALK) and MET tyrosine kinases.

8.1.4 Storage and Stability

Store at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F)

8.1.5 Dose Specifics

All patients will receive crizotinib or placebo 250 mg by mouth twice daily. The dose may be taken with or without food. Dose reductions are as follows: Dose level -1: 200 mg PO bid. Dose level -2: 250 mg PO daily.

8.1.6 Route of Administration

Oral route. Administer with or without food. Taking with food may decrease nausea. Capsules should be swallowed whole. Capsules should be taken roughly 12 hours apart. If the patient misses a dose, the dose should be taken as soon as it is remembered unless if the missed dose is within 6 hours of the next scheduled dose, then the missed dose should be skipped.

8.1.7 Drug/Food Interaction Information

Medications, herbals, or foods that are known potent CYP3A4 inhibitors should be avoided, including but not limited to amprenavir, atazanavir, clarithromycin, delavirdine, diltiazem, erythromycin, indinavir, itraconazole, ketoconazole, miconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, verapamil, voriconazole, and grapefruit or grapefruit juice

Medications, herbals, or foods that are known potent CYP3A4 inducers should be avoided, including but not limited to

carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, tipranavir, ritonavir, and St. John's wort

See Appendix V for a list of common CYP3A4 inducers or inhibitors which may affect crizotinib metabolism.

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8.1.8 Availability

Crizotinib and matching placebo are provided for free of charge by Pfizer and will be distributed by Patwell. Crizotinib is supplied in 250mg capsules with 50 capsules per bottle. The matching placebo will look exactly like the active drug but will contain inactive ingredients. Bottles of placebo will also contain 50 capsules. **The 200 mg capsules of crizotinib/placebo will be available only for patients who require a dose reduction.**

Drug Orders:

Initial Orders: Following submission of the required regulatory documents, and patient randomization to Step 1, a supply of crizotinib/placebo may be ordered from the ECOG-ACRIN Drug Team. Institutions must email the completed E4512 Crizotinib/Placebo Drug Request Form to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu or send by fax to 617-589-0919. A copy of the E4512 Crizotinib/Placebo Drug Request Form is located in Appendix VII of the protocol and is available for download from the E4512 Study Specific Tools section on the website (www.ecog.org). No blinded starter supplies are available.

Important information for drug orders:

At the time of randomization each patient will be assigned a patient specific Blinded Drug ID number, for example DR1117. The Blinded Drug ID number will appear on the patient's Confirmation of Registration Form.

The E4512 Crizotinib/Placebo Drug Request Form must include the patient specific Blinded Drug ID number with each drug request in order for the drug order to be processed. Failure to provide this information on the drug order form will result in a delay of the drug order being processed and shipped.

Due to the possibility of dose reductions the initial drug request for the 250 mg dose of crizotinib/placebo will be accompanied by a bottle of the 200 mg dose of the crizotinib/placebo. The 200 mg dose will be patient specific and should only be used in the event that the patient requires a dose reduction.

Due to the blinded treatment bottles of crizotinib and matching placebo MAY NOT be transferred from one patient to another patient.

Four bottles of crizotinib or matching placebo will be provided with each patient-specific shipment. Each bottle contains 50, 250 mg capsules.

Institutions should allow 3 business days for receipt of the crizotinib/placebo from the date the drug request is received by Patwell. Shipments will be made from Patwell Monday through Thursday for delivery onsite Tuesday through Friday.

There will be no weekend or holiday delivery of drugs.

Reorders:

Institutions should keep in mind that shipments take 3 business days from the date the drug request is received by Patwell. Reorders using the E4512 Crizotinib/Placebo Drug Request Form should be emailed to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu. Once the reorder is approved the drug will be received on site within 2-3 business days. Shipments will be made from Patwell on Monday through Thursday for delivery onsite Tuesday through Friday. **There will be no weekend or holiday delivery of drugs.**

The E4512 Crizotinib/Placebo Drug Request Form must include the patient specific Drug ID number that was assigned at the time of randomization in order for the drug order to be processed. Failure to provide this information on the drug order form will result in a delay of the drug order being processed and shipped.

Four bottles of crizotinib or matching placebo will be provided with each patient-specific shipment. Each bottle contains 50, 250 mg capsules. **If the patient has experienced a dose reduction following the previous drug order please indicate this on the form where applicable.**

Drug Inventory Records:

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

Drug Destruction and Return:

At the completion of each patient's treatment at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

Emergency Unblinding:

The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an **emergency or adverse event that may result in the need to unblind the patient.**

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. David E. Gerber, at (214) 648-4180, or Email: david.gerber@utsouthwestern.edu, first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operations Office – Boston drug team at (617) 632-3610 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., "E4512"), the patient ID number (e.g., "44444"), and the patient initials (e.g., "FL") to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment.

8.1.9 Side Effects

Cardiovascular effects: Bradyarrythmia, Chest discomfort, Edema Prolonged QT interval

Dermatologic effects: Rash

Gastrointestinal effects: Abdominal pain, Constipation, Decrease in appetite, Diarrhea, Disorder of esophagus, Nausea, Stomatitis, Taste sense altered, Vomiting

Hematologic effects: Lymphopenia, Neutropenia, Thrombocytopenia

Hepatic effects: ALT/SGPT level raised, AST/SGOT level raised, Hepatotoxicity, Serum bilirubin raised

Musculoskeletal effects: Arthralgia, Backache, Chest pain

Neurologic effects: Dizziness, Headache, Insomnia, Neuropathy

Ophthalmic effects: Disorder of vision

Respiratory effects: Cough, Dyspnea, Pneumonia, Pneumonitis, Pulmonary embolism, Upper respiratory infection

Other: Death, Fatigue, Fever

8.1.10 Nursing/Patient Implications

Crizotinib may cause nausea, vomiting. diarrhea or constipation. Treatment of GI adverse events may require standard anti-emetics such as prochlorperazine or ondansetron, or anti-diarrheal, or laxatives. Prophylactic antiemetics may be used.

Advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder, dizziness, or fatigue while taking crizotinib.

Patients should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study.

8.1.11 References

Product Information: XALKORI® oral capsules, crizotinib oral capsules. Pfizer Labs (per FDA), New York, NY, February 26, 2015.

Crizotinib Investigators Brochure, Pfizer, 2011.

8.2 Crizotinib, NSC #749005 – Open label, effective Addendum #8

8.2.1 Other Names

XALKORI®, PF 02341066

Chemical name: (R)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-pyridin-2-ylamine

8.2.2 Classification

Small molecule kinase inhibitor

8.2.3 Mode of Action

Crizotinib is a competitive inhibitor of the anaplastic lymphoma kinase (ALK) and MET tyrosine kinases.

8.2.4 Storage and Stability

Store at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F)

8.2.5 Dose Specifics

All patients randomized to Arm A (crizotinib) will receive crizotinib 250 mg by mouth twice daily. The dose may be taken with or without food. Dose reductions are as follows: Dose level -1: 200 mg PO bid. Dose level -2: 250 mg PO daily.

8.2.6 Route of Administration

Oral route. Administer with or without food. Taking with food may decrease nausea. Capsules should be swallowed whole. Capsules should be taken roughly 12 hours apart. If the patient misses a dose, the dose should be taken as soon as it is remembered unless if the missed dose is within 6 hours of the next scheduled dose, then the missed dose should be skipped.

8.2.7 Drug/Food Interaction Information

Medications, herbals, or foods that are known potent CYP3A4 inhibitors should be avoided, including but not limited to amprenavir, atazanavir, clarithromycin, delavirdine, diltiazem, erythromycin, indinavir, itraconazole, ketoconazole, miconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, verapamil, voriconazole, and grapefruit or grapefruit juice

Medications, herbals, or foods that are known potent CYP3A4 inducers should be avoided, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, tipranavir, ritonavir, and St. John's wort

See Appendix V for a list of common CYP3A4 inducers or inhibitors which may affect crizotinib metabolism.

8.2.8 Availability

Crizotinib is provided for free of charge by Pfizer and will be distributed by Patwell. Crizotinib is supplied in 250mg capsules with 50 capsules per bottle. **The 200 mg capsules of crizotinib will be available only for patients who require a dose reduction.**

Drug Orders:

Initial Orders: Following submission of the required regulatory documents, and patient randomization to Step 1, a supply of crizotinib may be ordered from the ECOG-ACRIN Drug Team. Institutions must email the completed E4512 Crizotinib Drug Request Form to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu or send by fax to 617-589-0919. A copy of the E4512 Crizotinib Drug Request Form is located in Appendix VII of the protocol and is available for download from the E4512 Study Specific Tools section on the website (www.ecog.org).

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Important information for drug orders:

The E4512 Crizotinib Drug Request Form must include the patient specific ID number with each drug request in order for the drug order to be processed. Failure to provide this information on the drug order form will result in a delay of the drug order being processed and shipped.

Due to the possibility of dose reductions the initial drug request for the 250 mg dose of crizotinib will be accompanied by a bottle of the 200 mg dose of the crizotinib The 200 mg dose will be patient specific and should only be used in the event that the patient requires a dose reduction.

Bottles of crizotinib MAY NOT be transferred from one patient to another patient.

Four bottles of crizotinib will be provided with each patient-specific shipment. Each bottle contains 50, 250 mg capsules.

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Institutions should allow up to 4 business days for onsite delivery of the crizotinib/placebo from the date the drug request is received by the E-A Drug Team. Patwell will ship and arrange drug deliveries to sites on business days only. There will be no weekend or holiday delivery of drugs.

There will be no weekend or holiday delivery of drugs.

Reorders:

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Institutions should keep in mind that shipments may take up to 4 business days from the date the drug request is received by the E-A Drug Team. Reorders using the E4512 Crizotinib/Placebo Drug Request Form should be emailed to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu. Once the reorder is approved the drug will be delivered to the site within 3-4 business days. Patwell will

ship and arrange drug deliveries to sites on business days only. There will be no weekend or holiday delivery of drugs.

The E4512 Crizotinib Drug Request Form must include the patient specific Drug ID number that was assigned at the time of randomization in order for the drug order to be processed. Failure to provide this information on the drug order form will result in a delay of the drug order being processed and shipped.

Four bottles of crizotinib will be provided with each patient-specific shipment. Each bottle contains 50, 250 mg capsules. **If the patient has experienced a dose reduction following the previous drug order please indicate this on the form where applicable.**

Drug Inventory Records:

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

Drug Destruction and Return:

At the completion of each patient's treatment at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

Unblinding of Patients Effective Addendum #8:

Once Addendum #8 has been posted on the ECOG-ACRIN and CTSU websites, site will unblind any patients that have previously enrolled to E4512. Sites may obtain unblinding information from the link provided in the activation memo of Addendum #8. Additionally, the unblinded treatment assignment can be obtained by calling a member of the ECOG-ACRIN Operations Office – Boston drug team at (857) 504-2900 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., "E4512"), the patient ID number (e.g., "44444"), and the patient initials (e.g., "FL") to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment. Once you have obtained the patient's treatment assignment, patients should be contacted with the information either by site contact or by using the "E4512 Addendum #8 Patient Letter" that can be found on the ECOG-ACRIN and CTSU websites.

Patients receiving placebo will continue to follow up per Section 5.1.2. Patients randomized to blinded crizotinib will continue to receive open label crizotinib.

8.2.9 Side Effects

Cardiovascular effects: Bradyarrythmia, Chest discomfort, Edema Prolonged QT interval

Dermatologic effects: Rash

Gastrointestinal effects: Abdominal pain, Constipation, Decrease in appetite, Diarrhea, Disorder of esophagus, Nausea, Stomatitis, Taste sense altered, Vomiting

Hematologic effects: Lymphopenia, Neutropenia, Thrombocytopenia

Hepatic effects: ALT/SGPT level raised, AST/SGOT level raised, Hepatotoxicity, Serum bilirubin raised

Musculoskeletal effects: Arthralgia, Backache, Chest pain

Neurologic effects: Dizziness, Headache, Insomnia, Neuropathy

Ophthalmic effects: Disorder of vision

Respiratory effects: Cough, Dyspnea, Pneumonia, Pneumonitis, Pulmonary embolism, Upper respiratory infection

Other: Death, Fatigue, Fever

8.2.10 Nursing/Patient Implications

Crizotinib may cause nausea, vomiting. diarrhea or constipation. Treatment of GI adverse events may require standard anti-emetics such as prochlorperazine or ondansetron, or anti-diarrheal, or laxatives. Prophylactic antiemetics may be used.

Advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder, dizziness, or fatigue while taking crizotinib.

Patients should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study.

8.2.11 References

Product Information: XALKORI® oral capsules, crizotinib oral capsules. Pfizer Labs (per FDA), New York, NY, February 26, 2015.

Crizotinib Investigators Brochure, Pfizer, 2011.

9. Statistical Considerations

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9.1 Study Design and Objectives

As of Addendum #8, the study will be an open label Phase III trial. Thus, all patients who were previously randomized to crizotinib versus placebo will be unblinded at the time of the amendment posting. All patients previously randomized to the placebo arm will be included as part of the observation arm in the statistical analysis. The design and sample size of the trial therefore remains the same.

This is a randomized phase III study evaluating the benefit of crizotinib (Arm A) as adjuvant therapy versus observation (Arm B) for patients with stage IB ≥ 4cm, II and IIIA, ALK-positive NSCLC following surgical resection. The primary objective of this trial is overall survival, and secondary objectives include disease-free survival and toxicity. Possible future correlative studies are subject to NCI approval and may include assessing whether the specific type of ALK fusion partner is associated with outcomes, and whether peripheral blood can be used to assess ALK positivity.

9.2 Study Endpoints

Overall survival (OS) is defined as the time from randomization to death from any cause. Patients that have not had an event reported at analysis will be censored at their date of last followup.

Disease-free survival (DFS) is defined as the time from randomization to the earliest event defined as:

- Disease recurrence confirmed by biopsy
- Any new lung cancer (even in the opposite lung) confirmed by biopsy
- Death from any cause at any known point in time

All deaths without a recurrence will be included as DFS events regardless of how long it has been since the last known disease evaluation. Patients with new primaries (other than lung) at other sites will be followed for disease recurrence of original cancer (the new non-lung primaries do not constitute recurrence.). Patients who have not had an event reported at the time of analysis will be censored at their date of last adequate disease evaluation defined as: time of CT. CT scans must be completed every 6 months in the first 2 years of protocol treatment every 12 months after 2-10 years from study registration.

Toxicity will be determined using the CTCAE version 4.0 criteria.

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9.3 Statistical Analysis Plan

The primary analysis will include all patients who testing positive for ALK at the central reference lab (Cancer Genetics), however patients with a local positive test but negative central test can still be randomized on the trial and will be included in a secondary analysis. Secondary analyses will typically include the primary analysis population. Exception to this include: analysis of toxicity data, which will include all patients from the primary analysis who received study drug regardless of eligibility.

OS and DFS distributions will be estimated using the Kaplan-Meier method, and Cox proportional hazards models will be used to estimate the treatment hazard ratios. The primary comparison of OS will use a logrank test stratified on the randomization stratification factors with a one-sided type I error rate of 5%. Other comparisons of groups will be made using the logrank test and Cox modeling.

Toxicity rates will be compared using Fisher's exact tests with a one-sided type I error rate of 5%; multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes.

Point estimates of all endpoints will be accompanied by the corresponding 90% confidence intervals.

In the event that there are missing data, no imputation of the missing data will be conducted. We will assume that data are missing at random and will conduct all analyses as originally planned because we do not anticipate an excess of missing data.

Subset analyses are planned for all stratification factors and all known prognostic factors such as performance status, age, gender, etc. Subset analyses of all variables are considered to be exploratory in nature.

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9.4 Sample Size Considerations

The primary comparison will include all randomized patients who tested positive for ALK at the central laboratory, of whom 360 will be accrued and randomized equally, for a total accrual of 180 patients per arm.

Using an overall one-sided 0.05 level logrank test, this study will have 80% power to detect a 33% reduction in the OS hazard rate of 0.0105 to 0.0070 based on the estimated accrual and follow-up period. Assuming exponential survival, this corresponds to a 50% improvement in the median OS of 66 months with observation alone to 99 months with crizotinib. The number of OS events needed to achieve this power is 164 events under the alternative hypothesis.

9.5 Projected Accrual

The phase I crizotinib trial accrued 82 advanced-stage patients at 7 institutions over two years. Given that this trial is expected to open nationwide at all of the cooperative groups, we have assumed an accrual rate of approximately 6 patients per month. It is estimated that the accrual goal of 360 patients for the primary analysis will be reached in approximately 60 months, with a follow-up period of approximately 42 months, making the study duration approximately 102 months (8.5 years). After an inflation of 5% for discordance between central and local testing, **the total number of patients to be accrued is 378 patients**.

9.6 Randomization Scheme

Randomization to treatment will be determined using permuted blocks within strata with dynamic balancing across the main institution plus affiliates. The randomization and the primary test will be stratified by stage at the time of resection (IB ≥ 4cm/II vs. IIIA), prior chemotherapy (yes vs. no), prior RT (yes vs. no), and gender (male vs. female).

9.7 Monitoring Plan

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee for efficacy, futility and safety. The study design incorporates a group sequential testing plan using a truncated O'Brien-Fleming boundary function at an overall one-sided significance level of 0.05 for assessing the stratified logrank test at each interim analysis. The O'Brien-Fleming group sequential boundary adjusts for the sequential testing and the use function methodology of Lan and DeMets will be employed to adjust the boundaries if the actual interim analyses do not correspond with the projected information times provided.

Power calculations assume a one-sided 0.05 level log-rank test and a truncated O'Brien-Fleming group sequential design (truncated at nominal significance level 0.001) with 10 interim analyses of OS starting at roughly 25% information (42 events under the alternative hypothesis) and one final analysis. Interim analyses will continue every six months corresponding to scheduled ECOG-ACRIN Data Safety Monitoring Committee meetings (at approximately 6-9% increments in information). The final interim analysis will occur at approximately 102 months after activation (164 events, under the alternative hypothesis). If the increment in information is less than 5%, an interim analysis will not be conducted.

If accrual proceeds according to expectation, four interim analyses will be performed before accrual is completed. More details of the planned interim analyses can be found in Table 1.

Table 1: Interim and final Analyses Characteristics for OS

Interim and final Analysis	% Information	Estimated Upper Boundary	Approximate Time (months)	Estimated Number of Events
1	25%	3.0902	41.5	42
2	32%	3.0902	47.5	53
3	40%	3.0902	53.5	66
4	49%	2.6534	59.5	81
5	58%	2.4120	65.5	95
6	66%	2.2489	71.5	108
7	74%	2.1256	77.5	121
8	81%	2.0283	83.5	133
9	88%	1.9493	89.5	144
10	94%	1.8839	95.5	154
Final	100%	1.8289	101.5	164

This study will also be monitored for early stopping in favor of the null hypothesis using repeated confidence interval methodology similar to that described by Jennison and Turnbull. At each interim analysis the nominal (1- 2 × alpha) confidence interval on the OS hazard ratio will be computed, where alpha is the nominal one-sided significance level of the use function boundary at the information fraction for the particular analysis time. If the confidence interval does not contain the target alternative of 0.67, then the data safety monitoring committee may consider terminating the study early for overall lack of treatment differences.

9.8 Gender and Ethnicity

Based on previous data from **E1505** the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	6	4	10
Not Hispanic or Latino	174	176	350
Ethnic Category: Total of all subjects	**180**	**180**	**360**

Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	4	5	9
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	16	16	32
White	158	157	315
Racial Category: Total of all subjects	**180**	**180**	**360**

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10. Sample Submissions

PATIENT CONSENT: Samples are to be submitted for optional laboratory research studies from patients who answer "Yes" to "*My samples and related information may be kept in a Biobank for use in future health research*."

LABELING: Specimens are to be labeled clearly with the ECOG-ACRIN protocol number "E4512", patient initials, date and time of collection, and sample type. All sample submissions are to be accompanied with an STS shipping manifest.

ALCHEMIST-SCREEN (ALLIANCE A151216) participation: All patients are required to be registered to A151216 prior to randomization. Pre-trial diagnostic tumor tissue must be submitted for central determination of ALK fusion status via ALCHEMIST-SCREEN (ALLIANCE A151216) either: a) Prior to randomization to E4512 to determine eligibility OR b) Within four weeks of randomization to E4512 Step 1 for central confirmation of locally determined ALK fusion status. Submission of blood and progression/recurrence tumor samples are also requested. Please refer to ALCHEMIST-SCREEN protocol (ALLIANCE A151216) for all submission instructions. Log the samples into the ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) for all submissions for A151216. Do not log or attempt to log these samples into the ECOG-ACRIN STS.

10.1 Blood Specimen Submissions to the ECOG-ACRIN CBPF

If these criteria cannot be met, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) (eacbpf@mdanderson.org) to obtain alternative submission requirements.

ECOG-ACRIN SAMPLE TRACKING SYSTEM (STS): All specimens submitted to the CBPF for E4512 must be entered and tracked using the ECOG-ACRIN Sample Tracking System. See Section 10.2.

10.1.1 Samples Preparation

Blood is to be collected at the following timepoints:

- After randomization, prior to start of treatment
- Cycle 5, prior to treatment
- Progression or relapse, whichever occurs first

It is requested that samples be batched at < -70°C and shipped on dry ice on a quarterly basis. If samples must be stored at -20°C ship on dry ice within 1 week of draw.

Draw the blood tubes in the following order: no anti-coagulant (red top or SST), potassium EDTA (EDTA, purple top). Note that vacutainer top color are for BD vacutainers. Verify tube contents prior to the collection of any samples.

Ship Frozen →

1. Serum
   - At each time point specified, draw one (1) 10mL vacutainer (no anti-coagulant)
   - Allow to coagulate at room temperature for 20 minutes
   - Separate by centrifugation at approximately 1200g x 20 minutes

- Aliquot serum into four cryovials. Discard residual cells
- Freeze the serum, at < -70°C preferred

Ship Frozen →

2. Plasma
   - At each time point specified, draw three (3) 10mL EDTA vacutainers
   - Separate by centrifugation at approximately 1200g x 20 minutes
   - Aliquot plasma into 12 cryovials.

Ship Frozen →

   - Replace the cap and
   - Freeze the plasma and residual cells (WBC + RBC) at < -70°C preferred

Ship Ambient →

3. Whole Blood, ACD DNA
   - At each time point specified, draw one (1) 10mL ACD DNA vacutainers
   - Ship at ambient

10.1.2 Shipping Guidelines

Specimens are to be shipped overnight on dry ice.

The receiving laboratory is not available to receive shipments over holidays or weekends. Therefore, samples are only to be shipped via overnight courier Sunday through Thursdays (excluding a day before a holiday).

Shipping Address

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

For submissions to the CBPF, site may use the CBPF's FedEx account using the FedEx On-Line Services. Access to the shipping account for specimen shipments to the CBPF at MD Anderson Cancer Center can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the CBPF by email at eacbpf@mdanderson.org. This account is for submissions to the CBPF ONLY

10.2 ECOG-ACRIN Sample Tracking System

NOTE: The ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) is required to be used for submissions on ALCHEMIST-SCREEN (ALLIANCE A151216) and the submission of tissue to NCI CCG Biospecimen Core. Do not log or attempt to log these samples into the ECOG-ACRIN STS.

All specimens submitted to the CBPF on E4512 must be entered and tracked using the ECOG-ACRIN Sample Tracking System.

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecogacrin.tst@jimmy.harvard.edu.

Study Specific Notes

SUBMISSIONS ON ALCHEMIST-SCREEN (ALLIANCE A151216) ARE NOT LOGGED OR TRACKED IN THIS SYSTEM.

If STS is unavailable at time of sample submissions for E4512, a completed Generic Specimen Submission Form (#2981) (Appendix IV) is to be submitted in lieu of the STS shipping manifest. Include site contact information on the form. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory the day of shipping. Indicate the appropriate Lab on the submission form:

ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

10.3 Use of Specimens in Research

Specimens submitted on E4512 from patients who consented to allow their specimens to be used for future research studies will be retained in an NCI-affiliated central repository designated above.

Request for the use of these specimens will require a correlative science proposal (or a protocol amendment) detailing the scientific hypothesis, research plan, assay methods for use of the biospecimens, and a complete statistical

section (with adequate power justification and analysis plan) which would be submitted and reviewed by the cooperative group and CTEP in accordance with the NCI National Clinical Trials Network (NCTN) review process.

Possible future studies include:

- Assessment of variants at diagnosis and resistance mechanisms at relapse
- Determination of the use of peripheral blood as a surrogate specimen for assessing ALK positivity

Specimens submitted will be processed to maximize their utility for research projects. Processing may include, but not limited to, extraction of DNA, isolation of plasma (if appropriate).

If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study. Tissue samples may be available for return upon written request and other samples may be destroyed per protocol of the given lab. Samples may also be anonymized (stripped of all identifiers) and used for instrument calibration or other quality control measures which are not published or linked to the clinical trial.

10.4 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office – Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office – Boston

11. Electronic Data Capture

Please refer to the E4512 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

11.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be conducted under an IND. All records pertaining to the trial (including source documents) must be maintained for:

- ☐ two years after the FDA approves the marketing application, or
- ☐ two years after the FDA disapproves the application for the indication being studied, or
- ☐ two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

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Appendix I

Pathology Submission Guidelines

Please refer to ALCHEMIST-SCREEN protocol (ALLIANCE A151216) for all tumor tissue submission instructions.

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Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again.

Sincerely,

[PHYSICIAN NAME]

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Appendix III

Patient Capsule Calendar

Capsule Calendar Directions

1. Take capsules as directed.
2. If you vomit anytime after taking a dose, do not “make it up” with an extra dose resume your next dose as scheduled.
3. If you forget, the missed capsules may be taken as long as it is more than 6 hours before your next dose.
4. Please bring the empty bottle or any leftover capsules and your capsule calendar to your next clinic visit.

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Patient Capsule Calendar for Crizotinib

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules that you take each day.** Take capsules as directed. If a dose is forgotten, it can be made up as long as it is taken more than 6 hours before your next dose. If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed capsule calendar to your doctor's visits.

Patient ID #: _____ **Drug Name:** Crizotinib

Dose: _____ **Cycle#:** _____

DAY	Date Month Day Year			Time capsules taken AM	 PM	Number of capsules taken AM	 PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
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A Randomized Phase III Trial for Surgically Resected Early Stage Non-Small Cell Lung Cancer: Crizotinib versus Observation for Patients with Tumors Harboring the Anaplastic Lymphoma Kinase (ALK) Fusion Protein

Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 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.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix V

Drugs Which May Affect Crizotinib Metabolism

The following is a list of common CYP3A4 inducers and inhibitors which may impact crizotinib metabolism. This is NOT a complete list of medications potentially incompatible with Crizotinib, therefore patient medications must be evaluated closely to determine patient eligibility for this trial.

List of CYP3A4 Inducing Agents:

Carbamazepine
Dexamethasone
Ethosuximide
Glucocorticoids
Griseofulvin
Modafinil
Naficillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbitol
Phenylbutazone
Phenytoin
Primidone
Progesterone
Rifabutin
Rifampin
Rifapentine
Rofecoxib
St. John's Wort
Sulfadimidine
Sulfinpyrazone
Tipranavir
Troglitazone

List of CYP3A4 Inhibitors:

Amiodarone
Cimetidine
Ciprofloxacin
Clarithromycin
Delavirdine
Diethyl-dithiocarbamate
Diltiazem
Erythromycin
Fluconazole
Fluvoxamine
Gestodene
Grapefruit or Grapefruit juice
Indanvir
Itraconazole
Ketoconazole
Mibefradil
Mifepristone
Nefazodone
Nelfinavir
Norfloxacin
Norfluoxetine
Ritonavir
Roxithromycin
Saquinavir
Troleandomycin
Voriconazole
Warfarin
Amprenavir
Atazanavir
Miconazole
Telithromycin
Verapamil

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Appendix VI

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Crizotinib, or within 28 days of the patient's last dose of Crizotinib must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS)

(http://ctep.cancer.gov/)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an amendment to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a new CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497, for it will need to be discussed on a case by case basis.

Reporting a Fetal Death

A fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

It must be reported via CTEP-AERS as Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions".

A fetal death should NOT be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the in utero exposure to Crizotinib must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "General disorders and administration - Other (neonatal loss)"under the System Organ Class (SOC) "General disorder and administration".

A neonatal death should NOT be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the CTEP 'Pregnancy Information Form' must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix VII

E4512 Crizotinib Drug Order Request Form

Section I (To be completed by Site) **All shaded areas must be completed before forwarding the drug request to the ECOG-ACRIN Drug Team.**	
ECOG-ACRIN Protocol Number:	**E4512**
Delivery Address **Institution Name:** **CTEP ID:** **Attention To:** **Street Address:** **City, State, Zip Code:**	**Shipment Must Reach Destination By:** **(MM/DD/YY) -** ***Institutions should allow up to 4 business days to receive drug onsite. Patwell will ship and arrange drug deliveries to sites on business days only, there will be no weekend or holiday deliveries***
Pharmacy Contact Name:	**Pharmacy Contact Phone:**
Pharmacy Contact Fax:	**Pharmacy Contact E Mail:**
Principal Investigator Name: **Principal Investigator Address:**	**PATIENT SEQUENCE NUMBER:** **PATIENT BLINDED DRUG ID#:**
Study Drug:	**Crizotinib**
Four bottles (4 cycles of treatment) will be provided with each shipment.	**Has the patient had a dose reduction since the last drug order request? (Circle) Yes No** **_____ 250 mg bottles _____ 200 mg bottles**
PLEASE EMAIL THIS DRUG REQUEST AS AN ATTACHMENT TO 900.drugorder@jimmy.harvard.edu or send by fax to (617) 589-0919	
Section II (To be completed by ECOG-ACRIN Drug Team)	
Cgroup/Inst/Affil: **CTEP ID:** **IRB Approval:** **Blinded Treatment confirmed:** **Personnel Name:** **Signature:** **Date:**	

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To Be Used with Addendum #8 (Open Label):
E4512 Crizotinib Drug Order Request Form
(For Patients Randomized to Arm A: Crizotinib)

Section I (To be completed by Site) All shaded areas must be completed before forwarding the drug request to the ECOG-ACRIN Drug Team.	
ECOG-ACRIN Protocol Number:	**E4512**
Delivery Address **Institution Name:** **CTEP ID:** **Attention To:** **Street Address:** **City, State, Zip Code:**	**Shipment Must Reach Destination By: (MM/DD/YY) –** **Institutions should allow up to 4 business days to receive drug onsite. Patwell will ship and arrange drug deliveries to sites on business days only,** there will be no weekend or holiday deliveries."
Pharmacy Contact Name:	**Pharmacy Contact Phone:**
Pharmacy Contact Fax:	**Pharmacy Contact E Mail:**
Principal Investigator Name: **Principal Investigator Address:**	**PATIENT SEQUENCE NUMBER:**
Study Drug: Crizotinib	
Four bottles (4 cycles of treatment) will be provided with each shipment.	**Has the patient had a dose reduction since the last drug order request? (Circle) Yes No** **_____ 250 mg bottles _____ 200 mg bottles**
PLEASE EMAIL THIS DRUG REQUEST AS AN ATTACHMENT TO 900.drugorder@jimmy.harvard.edu or send by fax to (617) 589-0919	
Section II (To be completed by ECOG-ACRIN Drug Team)	
Cgroup/Inst/Affil: **CTEP ID:** **Patient Randomized to Arm A:** **IRB Approval:** **Personnel Name:** **Signature:** **Date:**	

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Appendix VIII

ECOG-ACRIN Generic Specimen Submission Form: Form No. 2981v3

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments9/12/14