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
What is the purpose of the E4512 trial?

Currently, patients who are ALK negative experience greater overall survival than those who are ALK positive following surgical resection (Yang et al. J Thorac Oncol. 2012;7:90-97). This study compares the survival effects of using crizotinib after complete surgical resection versus observation in ALK-positive non–small cell lung cancer (NSCLC) patients.

What are all the objectives of E4512?

The primary objective of this trial is to evaluate whether adjuvant therapy with crizotinib will result in improved disease-free survival for patients with stage IB ≥ 4 cm, II, and non-squamous IIIA, ALK-positive NSCLC following surgical resection. The secondary objectives consist of 3 aims: to evaluate and compare overall survival associated with crizotinib, to evaluate the safety profile of crizotinib when given in the adjuvant therapy setting, and to collect tumor tissue and blood specimens for future research.

Must all patients be ALK positive to participate in E4512?

Yes, all patients must be ALK positive to take part in the trial, as the agent under investigation was previously shown to be effective in improving response rate, progression-free survival, and 1-year survival rate in patients with ALK-positive advanced NSCLC.

What testing procedures are acceptable to determine ALK status?

ALK fusion status can be determined by local Clinical Laboratory Improvement Amendments of 1988 (CLIA)–certified labs and centrally via ALCHEMIST-SCREEN trial (A151216).

All patients must have received a complete surgical resection. What forms of resection are acceptable?

The accepted types of resection with negative margins include lobectomy, sleeve lobectomy, bilobectomy, pneumonectomy, intrapericardial pneumonectomy, wedge resection, or segmentectomy.
How much time must have passed between surgery and randomization?

All patients must have adequately recovered from surgery at the time of randomization, with a minimum time between date of surgery and randomization of at least 4 weeks. The maximum time between surgery and randomization must be 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.

E4512 is part of a clinical trial platform. What is the goal of this platform?

E4512 is 1 of the 4 protocols involved in the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST). This platform aims to develop the use of adjuvant targeted therapies for genotype-defined lung cancer populations.

What are the names and significance of the other 3 ALCHEMIST trials?

The 4 trials that make up the ALCHEMIST platform are highly integrated. In addition to ALCHEMIST-ALK (E4512), the platform includes ALCHEMIST-EGFR (epidermal growth factor receptor), or A081105, which is a randomized study of adjuvant erlotinib versus observation in EGFR-mutant lung adenocarcinoma. ALCHEMIST-ANVIL, or EA5142, is a randomized trial of adjuvant nivolumab for patients not eligible for E4512 or A081105. ALCHEMIST-SCREEN, or A151216, is the platform trial to which all participants must consent and will perform central genotyping of EGFR and ALK (anaplastic lymphoma kinase); this trial will also collect additional tissue for advanced genomic analysis and clinically follow patients not participating in the named trials.

Is it mandatory for patients registered to E4512 to take part in an additional trial?

Yes, prior to randomization, patients in E4512 must also be registered to the ALCHEMIST-SCREEN (ALLIANCE A151216) trial. Prediagnostic tumor specimens must also be submitted for ALK fusion status assessments.
What is the treatment plan for E4512?

Patients will be randomized to receive crizotinib 250 mg PO bid on a continuous dosing schedule during days 1 to 21 (cycle = 21 days) or observation. Treatment will continue until recurrence, unacceptable toxicity, or up to 2 years. Follow-up will continue for 10 years.

What are the treatment and follow-up durations of E4512?

Trial participants will receive treatment for a maximum of 2 years from randomization unless the following occur: extraordinary medical circumstances, withdrawal of consent, evidence of recurrent NSCLC, development of second primary (including a second lung primary), but not including squamous or basal cell carcinoma of the skin, in situ of the cervix, unacceptable toxicity requiring discontinuation of treatment, a need for treatment delay for more than 6 weeks due to lack of toleration, global deterioration of health-related symptoms, protocol noncompliance, or pregnancy. All patients, including those who discontinue therapy early, will be followed for recurrence (even if nonprotocol therapy is initiated) and for survival for 10 years from the date of registration.

How are the patients monitored?

Each patient will be required to have an electrocardiogram and a height measurement at screening. Patients must also complete a physical exam, medical history, toxicity assessment, imaging, and monitoring of weight, blood pressure, heart rate, liver, serum, and complete blood count before and during the trial. Imaging studies, specifically CT or MRI, are preferred over evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease. In addition, cytology and histologic techniques can be used to differentiate between complete and partial response in rare cases. Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required.
How can crizotinib be ordered?

A drug order request form, located at the end of the protocol, must be completed and e-mailed or faxed. The request must then be approved and agents will be sent.

For Further Study Information

• For more information about the E4512 study, please visit the following:
  – Cancer.gov; search E4512
  – Clinicaltrials.gov; search NCT02201992
• For more information about ECOG-ACRIN visit ecog-acrin.org