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

Study Schema

Eligibility:
- ALK positive
- Stage IB (≥ 4 cm)/II/IIIA NSCLC
- Complete surgical resection*
- Patient registered to ALCHEMIST Screening Trial (A151216)

Stratification:
- Stage: IB ≥ 4 cm/II vs IIIA
- Prior radiation therapy: yes vs no
- Gender: male vs female

Arm A‡
Crizotinib
- 250 mg PO bid
Treatment will continue until recurrence, unacceptable toxicity, or up to 2 years

Arm B†
Observation

Step 1

Accrual goal = 168 patients.
Cycle = 3 weeks (21 d).
Prior to activation of Addendum 8, arm B patients were receiving placebo.
*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.
†All patients participating in E4512 must be registered to ALCHEMIST-SCREEN (ALLIANCE A151216), and pretrial diagnostic tumor specimens must be submitted for ALK fusion status assessments.
‡Crizotinib will be administered PO bid at 250 mg, approximately the same time each day on a continuous daily dosing schedule, ie, no break in dosing (days 1-21). Doses should be taken 12 hours apart.
ALK = anaplastic lymphoma kinase; NSCLC = non–small cell lung cancer.

Long-term follow-up
E4512: ALCHEMIST Study

Overall E4512 Study Objective

To determine whether the use of crizotinib compared with observation in the adjuvant therapy setting will provide a survival benefit in patients with resected, ALK-positive, early-stage non–small cell lung cancer (NSCLC)

Study Objectives

Primary Objective

• Evaluate whether adjuvant therapy with crizotinib will result in improved disease-free survival for patients with stage IB ≥ 4 cm, II, and IIIA, ALK-positive NSCLC following surgical resection

Secondary Objectives

• Evaluate and compare overall survival associated with crizotinib
• Evaluate the safety profile of crizotinib when given in the adjuvant therapy setting
• Collect tumor tissue and blood specimens for future research

Eligibility Criteria*

Main Inclusion Criteria

• ≥ 18 years of age
• Undergone complete surgical resection of stage IB ≥ 4 cm, II, or non-squamous IIIA NSCLC per American Joint Committee on Cancer 7th edition and have had negative margins. N3 disease is not allowed
• Baseline chest CT with or without contrast must be performed within 6 months (180 d) prior to randomization to ensure no evidence of disease. If clinically indicated, additional imaging studies must be performed to rule out metastatic disease
• ECOG performance status of 0 or 1
• Registered to ALCHEMIST-SCREEN (ALLIANCE A151216) trial prior to randomization

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
• Positive for translocation or inversion events involving the ALK gene locus (eg, resulting in EML4-ALK fusion) as defined by a Clinical Laboratory Improvement Amendments of 1988 (CLIA)—approved test, including (1) translocation or inversion events involving the ALK gene locus (eg, 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
  – Must have been performed by a local CLIA-certified laboratory or patient registered to, and the ALK fusion status performed centrally on, the ALCHEMIST-SCREEN (ALLIANCE A151216)
• Adequately recovered from surgery at time of randomization: minimum time between date of surgery and randomization must be at least 4 weeks; maximum time between surgery and randomization must be 3 months if no adjuvant chemotherapy was administered, 8 months if adjuvant chemotherapy was administered, or 10 months if adjuvant chemotherapy and radiation were administered
• Completion of any prior adjuvant chemotherapy or radiation therapy 2 or more weeks (6 or more wk for mitomycin and nitrosoureas) prior to randomization and adequate recovery at time of randomization
  – Patients taking low-dose methotrexate for nonmalignant conditions and other cytotoxic agents for nonmalignant conditions are allowed to continue treatment while on study
• Recovered from any nonhematologic toxicity from surgery, chemotherapy, or radiation to grade ≤ 1, with the exception of alopecia
• Adequate organ and marrow function
• Use of effective contraception
Eligibility Criteria* (Cont)

Main Exclusion Criteria

- 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 or social situations that would limit compliance with study requirements
- Known interstitial fibrosis or interstitial lung disease
- Prior treatment with crizotinib or another ALK inhibitor
- Ongoing cardiac dysrhythmias of grade ≥ 2 NCI CTCAE version 4.0, uncontrolled atrial fibrillation (any grade), or QTc interval > 470 msec

- Use of medications, herbals, or foods that are known potent CYP3A4 inhibitors or inducers
- History of locally advanced or metastatic cancer requiring systemic therapy within 5 years from randomization, except in situ carcinomas and nonmelanoma skin cancer; no previous primary lung cancer diagnosed concurrently or within the past 2 years
- Receiving any other investigational agents while on study
- Pregnancy or breast-feeding

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.