ALCHEMIST
(Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials)

3 Integrated Trials Testing Targeted Therapy in Early Stage Lung Cancer

Part of NCI’s Precision Medicine Effort in Cancer

August 2014
NCI: Developing a National Strategy for Precision Medicine

• Help advance molecular profiling from research use into the clinic

• Genotype to Phenotype:
  • Develop portfolio of trials across spectrum from early stage to advanced disease
  • Screen for molecular features that may predict response to a drug with a given mechanism of action
  • Analyze tumor specimens at relapse to define mechanisms of resistance
  • Develop public database that links clinical outcomes with molecular tumor characteristics for continued research

• Phenotype to Genotype:
  • Identify molecular mutations/changes in gene expression that explain why patients responded to a treatment that did not work for others
ALCHEMIST Background

- ALCHEMIST will evaluate molecularly targeted therapy in early stage Non-Small Cell Lung Cancer (NSCLC) with non-squamous histologies (e.g., adenocarcinoma, large cell carcinoma) that has been completely surgically resected.

- Molecularly targeted therapy has improved outcomes within these histologies in advanced NSCLC:
  - erlotinib (target: EGFR activating mutation)
  - crizotinib (target: EML4-ALK)

- This has led to routine testing of EGFR mutations and ALK rearrangement in advanced disease.

- However, patients treated with Tyrosine Kinase Inhibitors eventually develop resistance.
Drug Biomarkers in Lung Adenocarcinoma

- **TKI-sensitizing EGFR mutations:**
  - 10% in Western population
  - Up to 50% in Asian population
  - Enriched in:
    - females
    - non-smokers
    - younger patients
- **Multiple tests in clinical use**
  http://www.mycancergenome.org/content/disease/lung-cancer/egfr/5)

- **ALK Rearrangement:**
  - 5-7% in Western population
  - FDA approved companion diagnostic:
  - Vysis Break Apart FISH assay
  (ALK estimate: Kwak, EL. NEJM 2010)
**The Drugs: Obvious Effects**

**Erlotinib (Astellas):**
- Initial indication not marker-specific
  - 2nd line adv/met NSCLC
  - maintenance in adv/met
  - new: 1st line met with EGFR mutations
- EURTAC Phase III
  - 1st line adv/met NSCLC
  - 1227 screened
  - 173 randomized

**Crizotinib (Pfizer):**
- Exceptional Responses
- mPFS 10 mo

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2+ line, metastatic RR 57%

Rosell, Lancet Onc. 13:3; 2012

Kwak, NEJM 363:1693; 2010
ALCHEMIST Rationale

• ALCHEMIST is studying whether or not treatment based on genotype improves cure rates in earlier stage (IB-IIIA) NSCLC cancer patients with non-squamous tumors that have been completely surgically resected.
ALCHEMIST Structure

ALCHEMIST is an integrated research effort with 3 component trials:

1. **Screening Trial - A151216:** Eligible patients will have their tumor tissue tested for genetic changes in ALK or EGFR. If tissue testing is positive, they will be referred to one of the treatment trials. If negative, they will be followed for 5 years. All patients contribute information to the national public resource for research.

2. **Erlotinib Treatment Trial - A081105:** Erlotinib vs. placebo will be evaluated in patients with activating EGFR mutations following standard of care adjuvant therapy.

3. **Crizotinib Treatment Trial - E4512:** Crizotinib vs. placebo will be evaluated in patients harboring the Anaplastic Lymphoma Kinase (ALK) fusion protein following standard of care adjuvant therapy.
ALCHEMIST Design

• ALCHEMIST is designed to accommodate evolving clinical science and research opportunities. Evaluation of other targeted therapies could be added to the research effort in the future as new and promising therapies emerge.
ALCHEMIST Leadership

• Integrated leadership for the ALCHEMIST research effort by the NCI National Clinical Trials Network (NCTN) Groups
  - Alliance for Clinical Trials in Oncology
  - ECOG-ACRIN Cancer Research Group
  - NRG Oncology
  - SWOG

• Alliance is the lead coordinating center for the ALCHEMIST Screening (A151216) & EGFR Treatment Trials (A081105) and ECOG-ACRIN is the lead coordinating center for the ALK Treatment Trial (E4512)

• Trials open to all US institutions/sites in the NCTN and in the NCI Community Oncology Research Program Network (NCORP)
• Agents are being supplied for the treatment trials by Astellas (erlotinib) and Pfizer (crizotinib).

• Testing for EGFR and ALK is funded by NCI and will be performed in a central laboratory by Response Genetics, Inc.

• Research effort with advanced genomic analysis by the NCI Center for Cancer Genomics (CCG)
ALCHEMIST Screening Trial Goals: Clinical

• Conduct one integrated program for screening the target patient (early stage) population to identify:
  • EGFR mutations
  • ALK rearrangements

• Patients can then be enrolled on 1 of 2 specific adjuvant trials testing the benefit of adding Erlotinib (EGFR) or Crizotinib (ALK) therapy after standard adjuvant therapy prescribed by the patients’ treating physicians

• Define the clinical and biologic/molecular behavior of tumors that do not harbor the targeted molecular alterations
ALCHEMIST Screening Trial Goals: Genomic

• Research component addressing all patients:
  • The ALCHEMIST Screening Trial is collecting clinically annotated tumor tissue and patient-matched germline DNA (from blood) from all patients screened
  • Samples collected will undergo advanced genomic analysis by the NCI Center for Cancer Genomics (CCG)
  • Study will collect clinical follow-up data & detailed epidemiologic data
  • When possible, a sample at recurrence will be collected.

• Provides public resource for research community with genomic characterization tied to detailed clinical annotation, epidemiology data, & long-term outcome data
Patient Pre-Registration Eligibility Criteria

• Diagnosis of NSCLC (non-squamous)

  *Pre-Operative*: Clinical stage IB ($\geq 4$ cm) – IIIA

  *or* *Post-Operative*: Pathologic stage IB ($\geq 4$ cm) – IIIA

Patient Eligibility Criteria

• Complete surgical resection (negative margins)
• Adequate tissue for EGFR/ALK testing
• Adequate tissue/blood for NCI CCG genomic research component
• Positive local test of EGFR or ALK alterations allowed
ALCHEMIST-SCREENING Trial Schema

Trials conducted at sites in the NCI Clinical Trials Networks: NCTN & NCORP

Non-squamous NSCLC (n=6,000 to 8,000 pts)
Clinical/Pathologic Stage IB (≥ 4cm), II, IIIA
Post-Op cohort with negative surgical margins

Pre-op cohort
Post-op cohort

Complete resection + standard adj therapy per treating physician

Central EGFR & ALK genotyping

EGFR-mutation: Phase III trial of erlotinib vs placebo x 2 years (n=410) after any adj tx

ALK-rearranged: Phase III trial of crizotinib vs placebo x 2 years (n=360) after any adj tx

Without Molecular Alterations: Followed q6 months x 5 years after any adj tx

FFPE tissue & blood specimen

Advanced genomics at the NCI

FFPE tissue from biopsy done at recurrence
ALCHEMIST Treatment Trials Eligibility

- Patients must be registered to the ALCHEMIST SCREENING Trial (A151216) prior to randomization to the treatment trials

- Patients with a tumor positive for activating EGFR mutations (eligible for A081105)

- Patients with a tumor positive for translocation or inversion of the ALK gene (eligible for E4512)

- Must have undergone complete surgical resection of their stage IB (≥ 4 cm), II, or IIIA NSCLC per AJCC 7th edition and with negative tumor margins

- Must have completed their standard of care chemotherapy or chemotherapy and radiation therapy as prescribed by their treating physician
Primary endpoint is overall survival

Resected NSCLC tissue tested on ALCHEMIST Screening Trial

Patients with tumors with an EGFR mutation

RANDOMIZE

1 cycle = 21 days

Erlotinib 150 mg once a day x 2 years

Placebo once a day x 2 years

Long Term Follow-up

Long Term Follow-up
Resected NSCLC tissue tested on ALCHEMIST Screening Trial

Patients with tumors with an ALK re-arrangement

Randomize

Primary endpoint is overall survival

1 cycle = 21 days

Crizotinib 250 mg po BID x 2 years

Long Term Follow-up

Placebo po BID x 2 years

Long Term Follow-up
### ALCHEMIST– Statistical Design Elements

<table>
<thead>
<tr>
<th>Trial Category</th>
<th>ALCHEMIST Screening Trial A151216</th>
<th>ALCHEMIST EGFR Treatment Trial A081105 (± erlotinib)</th>
<th>ALCHEMIST ALK Treatment Trial E4512 (± crizotinib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Registry/Intervention with biopsy at recurrence</td>
<td>EGFR mutation</td>
<td>ALK rearrangement</td>
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<tr>
<td>Prevalence of Target</td>
<td>~10%</td>
<td>~5%</td>
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<tr>
<td>Total Sample Size</td>
<td>6000 – 8000</td>
<td>430 (5% ineligible)</td>
<td>378 (5% ineligible)</td>
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<td>Primary Endpoint</td>
<td>Correlative endpoints &amp; epidemiology</td>
<td>Overall survival</td>
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<td>Power</td>
<td>85%</td>
<td>80%</td>
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<td>One-sided α</td>
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<tr>
<td>Hazard Ratio</td>
<td>0.67</td>
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ALCHEMIST Additional information

ALCHEMIST information available on www.clinicaltrials.gov

- **ALCHEMIST - Screening Trial (A151216)**
  Coordinated by the ALLIANCE
  ClinicalTrials.gov Identifier: NCT02194738
  Principal Investigators: Pasi A. Jänne, MD, PhD & Geoffrey Oxnard, MD

- **ALCHEMIST - EGFR Treatment Trial (A081105)**
  Coordinated by the ALLIANCE
  ClinicalTrials.gov Identifier: NCT02193282
  Principal Investigator: Ramaswamy Govindan, MD

- **ALCHEMIST - ALK Treatment Trial (E4512)**
  Coordinated by ECOG-ACRIN
  ClinicalTrials.gov Identifier: NCT02201992
  Principal Investigator: David Gerber, MD
ALCHEMIST is open to all sites that participate in the NCI National Clinical Trials Network (NCTN) or NCI Community Oncology Research Program (NCORP)

To Register Patients, Please Visit www.ctsu.org