National Cancer Institute

NCTN NCI National Clinical Trials Network
Research Driving Progress

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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

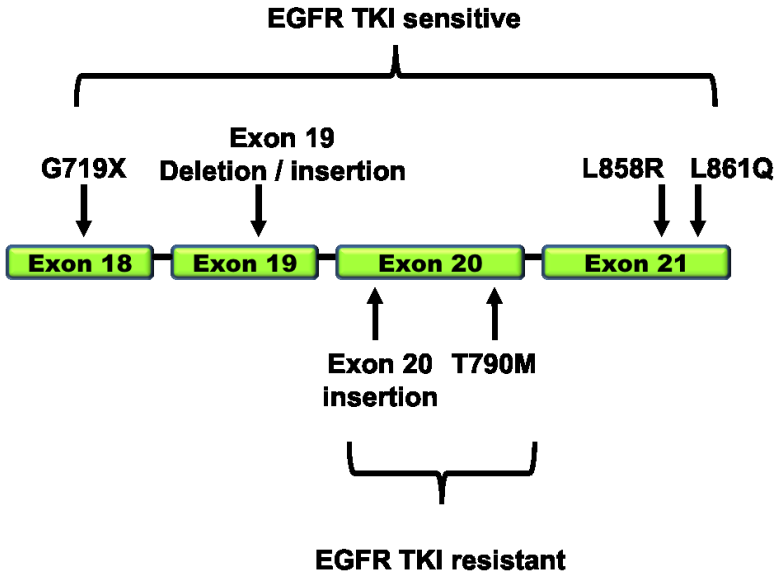
ALCHEMIST Background

- **ALCHEMIST will evaluate molecularly targeted therapy in early stage Non-Small Cell Lung Cancer (NSCLC) with non-squamous histologies (i.e., adenocarcinoma, large cell carcinoma, etc.) 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 lead 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

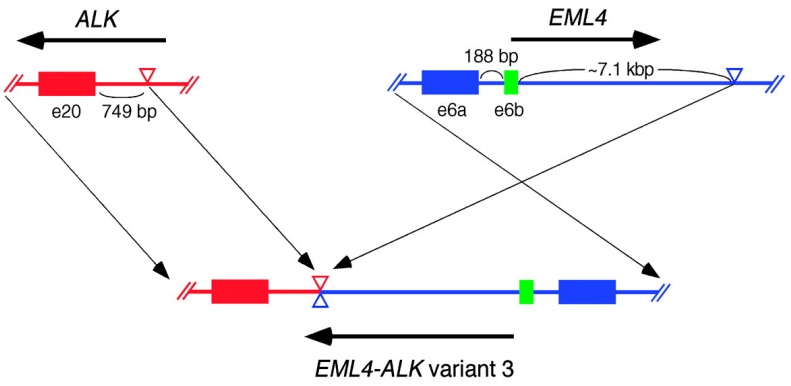
- **TKI-sensitizing EGFR mutations:**
- **10% in Western population**
- **Up to 50% in Asian population**
- **Enriched in:**
  - females
  - non-smokers
  - younger patients
- **Multiple tests in clinical use**

  (EGFR estimate: Hirsch, FR. Lancet Oncol 2009 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**

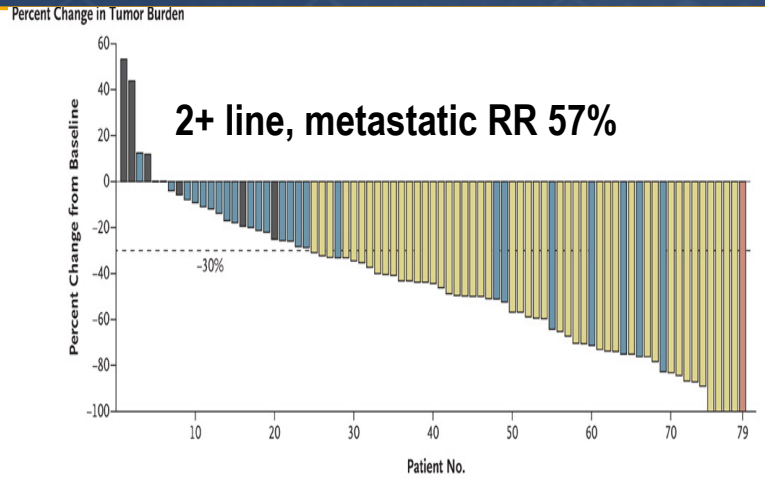
  (ALK estimate: Kwak, EL. NEJM 2010)



The Drugs: Obvious Effects

Crizotinib (Pfizer):

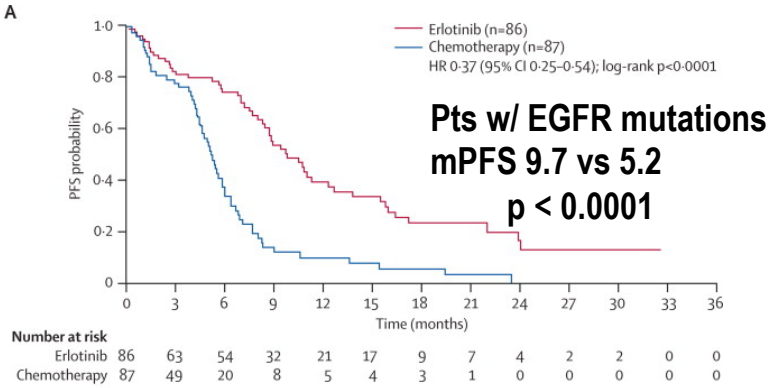
- **Exceptional Responses**
- **mPFS 10 mo**



Kwak, NEJM 363:1693; 2010

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



Rosell, Lancet Onc. 13:3; 2012

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)**

ALCHEMIST Support

- Agents are being supplied for the treatment trials by Astellas (erlotinib) and Pfizer (crizotinib)
- Testing for ALK and EGFR 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**

ALCHEMIST Screening Trial Eligibility

Patient Pre-Registration Eligibility Criteria

- Diagnosis of NSCLC (non-squamous)

Pre-Operative: Clinical stage IB (≥4 cm) – IIIA

or *Post-Operative*: Pathologic stage IB (≥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

→ FFPE tissue & blood specimen

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

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

→ <u>Without Molecular Alterations</u>: Followed q6 months x 5 years after any adj tx

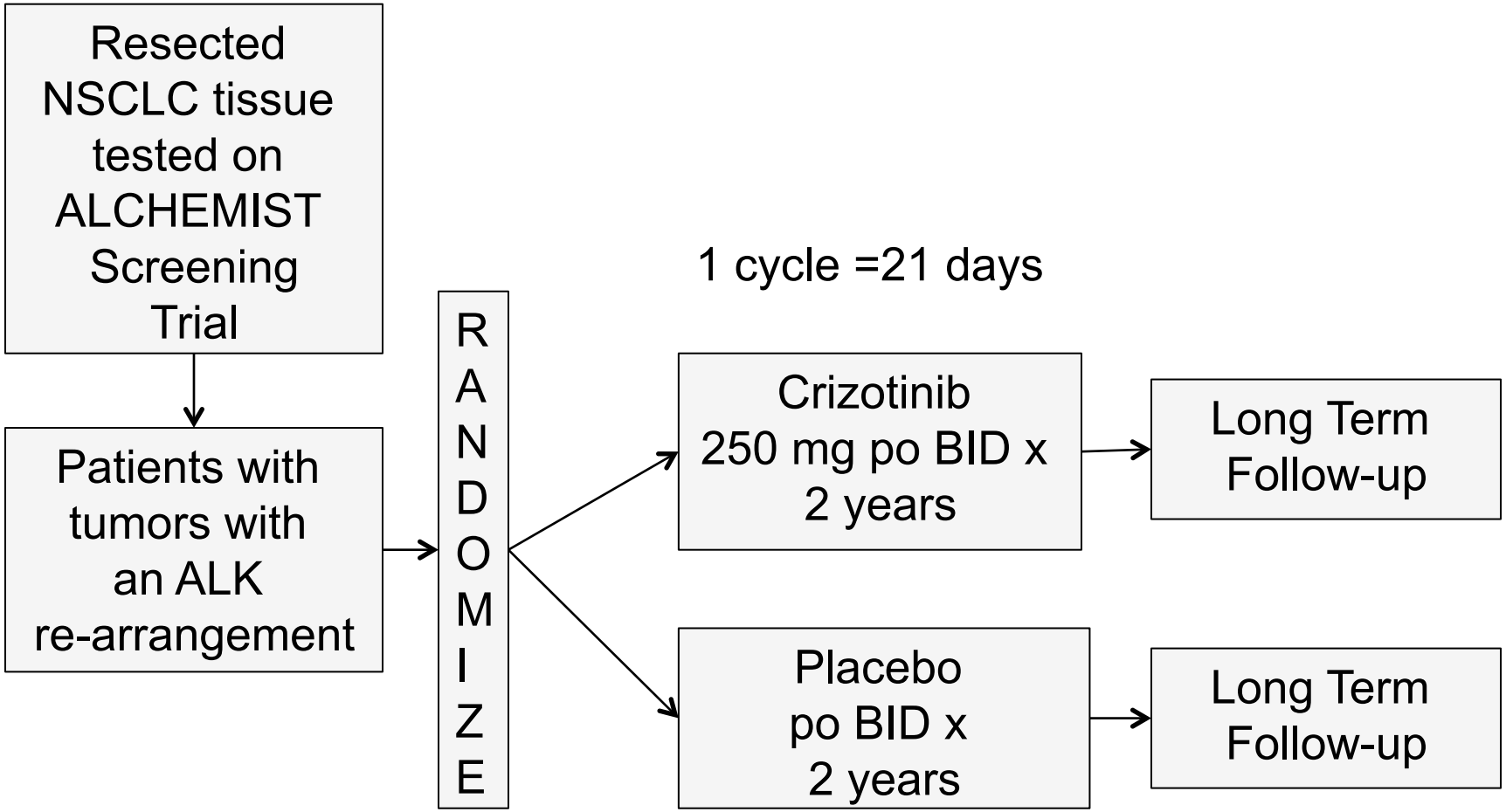
FFPE tissue from biopsy done at recurrence

Advanced genomics at the NCI

ALCHEMIST Treatment Trials Eligibility

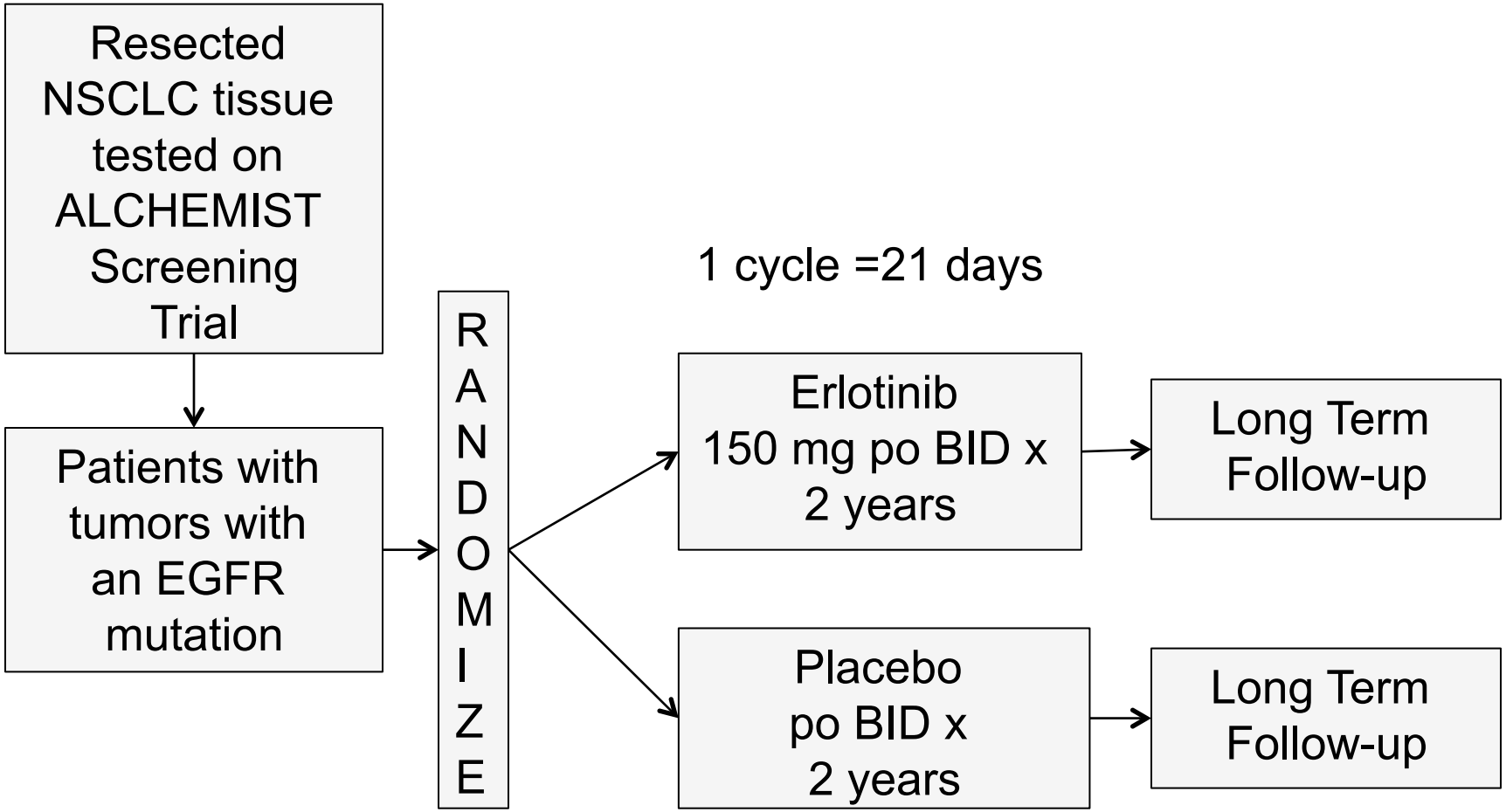
- Patients must be registered to the ALCHEMIST SCREENING Trial (A151216) prior to randomization to the treatment trials
- Patients with a tumor positive for translocation or inversion of the ALK gene (*eligible for E4512*)
- Patients with a tumor positive for activating EGFR mutations (*eligible for A081105*)
- 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

ALCHEMIST ALK Treatment Trial E4512



Primary endpoint is overall survival

ALCHEMIST EGFR Treatment Trial A081105



Primary endpoint is overall survival

ALCHEMIST– Statistical Design Elements

Trial Category	ALCHEMIST Screening Trial A151216	ALCHEMIST ALK Treatment Trial E4512 (± crizotinib)	ALCHEMIST EGFR Treatment Trial A081105 (± erlotinib)
Target	Registry/Intervention with biopsy at recurrence	ALK rearrangement	EGFR mutation
Prevalence of Target		~5%	~10%
Total Sample Size	6000 – 8000	378 (5% ineligible)	430 (5% ineligible)
Primary Endpoint	Correlative endpoints & epidemiology	Overall survival	Overall survival
Power		80%	85%
One-sided α		0.05	0.05
Hazard Ratio		0.67	0.67

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

Registration Information

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"


DEPARTMENT OF HEALTH & HUMAN SERVICES · USA


NIH


NATIONAL®
CANCER
INSTITUTE