ALCHEMIST Trials: A Golden Opportunity to Transform Outcomes in Early-Stage Non–Small Cell Lung Cancer

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Abstract

The treatment of patients with metastatic non–small cell lung cancer (NSCLC) is slowly evolving from empirical cytotoxic chemotherapy to personalized treatment based on specific molecular alterations. Despite this 10-year evolution, targeted therapies have not been studied adequately in patients with resected NSCLC who have clearly defined actionable mutations. The advent of next-generation sequencing has now made it possible to characterize genomic alterations in unprecedented detail. The efforts begun by The Cancer Genome Atlas project to understand the complexities of the genomic landscape of lung cancer will be supplemented further by studying a large number of tumor specimens. The Adjuvant Lung Cancer Enrichment Markers Identification and Sequencing Trial (ALCHEMIST) is an NCI-sponsored national clinical trials network (NCITN) initiative to address the needs to refine therapy for early-stage NSCLC. This program will screen several thousand patients with operable lung adenocarcinoma to determine whether their tumors contain specific molecular alterations [epidermal growth factor receptor mutation (EGFR) and anaplastic lymphoma kinase rearrangement (ALK)], making them eligible for treatment trials that target these alterations. Patients with EGFR mutation or ALK gene rearrangement in their tumor will be randomized to placebo versus erlotinib or crizotinib, respectively, after completion of their standard adjuvant therapy. ALCHEMIST will also contain a large discovery component that will provide an opportunity to incorporate genomic studies to fully understand the clonal architecture, clonal evolution, and mechanisms of resistance to therapy. In this review, we describe the concept, rationale, and outline of ALCHEMIST and the plan for genomic studies in patients with lung adenocarcinoma. Clin Cancer Res; 21(24): 5439–44. © 2015 AACR.

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Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States (1). Adenocarcinoma of the lung is the most commonly diagnosed histologic subtype of non–small cell lung cancer (NSCLC; ref. 2). The advent of targeted therapies, specifically those directed towards EGFR mutation and anaplastic lymphoma kinase (ALK) rearrangement, have improved outcomes in a subset of patients with advanced NSCLC (3–6). However, the role of molecular testing and targeted therapies for earlier-stage disease remains unclear. Specifically, prospective randomized studies focused on patients with EGFR-mutant or ALK-positive completely resected stage I–III NSCLC have not been conducted to date.

Nearly a third of patients with NSCLC have a potentially curable early-stage disease. Adjuvant cisplatin-based doublet chemotherapy has been shown to improve overall survival by 4% to 15% in patients with stage I–III NSCLC (7–9). The data from the LACE meta-analysis confirmed a 5.4% overall survival (OS) benefit at 5 years with adjuvant chemotherapy compared with observation [HR, 0.89; 95% confidence interval (CI), 0.82–0.96; ref. 10]. However most of the benefit seems to be restricted to patients with stage II and III NSCLC. Adjuvant postoperative chemotherapy has become the standard of care in patients with resected stage II to III NSCLC. Despite the use of postoperative chemotherapeutic, nearly a third of patients with stage I NSCLC and at least 30% to 50% of patients with stage II and III NSCLC will still die from recurrent disease. Thus, a significant need remains to improve the outcomes in these patients.

It has become apparent in recent years that lung cancer in general and adenocarcinoma in particular is a molecularly diverse disease. Even though several pathways appear to be dysregulated at a given time, it is widely believed that some cancer cells become “addicted” to certain pathways more than others (oncogene addiction). These pathways are potentially valuable targets for therapy. The improvements seen with imatinib in advanced gastrointestinal stromal tumor (GIST) and trastuzumab in metastatic breast cancer led to the investigation of these drugs in early-stage disease to improve cure rates (11, 12). We believe the time is ripe now to develop a durable and long-term strategy to evaluate targeted therapies in carefully selected groups of patients based on the tumor genotype following surgical resection to cure more patients with lung cancer. Molecularly targeted therapies have not yet been shown to improve OS in patients in this setting. Ongoing studies in Asia are evaluating the superiority of EGFR tyrosine kinase inhibitors (TKI) in patients with resected NSCLC compared with cytotoxic chemotherapy (e.g., NCT02448797, NCT01405079). The NCTN mechanism is uniquely suited to address this issue by facilitating genomic screening nation-wide that will allow serial investigation of a number of new compounds in clearly defined subsets of patients with resected NSCLC.

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Ongoing work from The Cancer Genome Atlas (TCGA) has clearly demonstrated the complexity of lung adenocarcinoma (13, 14). Given the extent of background mutations present in the lung adenocarcinoma tumor specimens from years of tobacco smoking, several thousand tumors need to be analyzed using high-throughput DNA testing to discover rare alterations (15). Moreover, secondary drivers present in tumors initiated by canonical alterations in EGFR and ALK have not been carefully identified. In addition, it is critical to understand the clonal evolution following exposure to targeted therapies.

It is obvious that a robust clinical trial infrastructure needs to be developed to prospectively genotype patients with early-stage NSCLC to evaluate the role of specific molecularly targeted agents in this setting. In addition, the samples from appropriately consented individuals should be utilized to study the complexity of lung adenocarcinoma genomes in great detail as a means to identify low frequency variants and develop prognostic and predictive models based on molecular subsets. Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) is the NCI sponsored NCTN initiative to address these needs. We describe here the rationale, schema, and design of the proposed studies.

ALCHEMIST Overview

ALCHEMIST is a clinical trial platform to facilitate identification, enrollment, and treatment of genotype-selected patients with resected nonsquamous NSCLC in trials of genotype-directed adjuvant therapy. The choice of nonsquamous NSCLC is driven by the presence of actionable mutations with drugs of proven efficacy in the advanced-disease setting. At the present time of its activation, ALCHEMIST consists of three integrated protocols, with additional protocols anticipated/planned in the future.

ALCHEMIST Screening (A151216) is the platform trial to which all patients must consent in order to be considered for ALCHEMIST therapeutic trials. On this protocol, the tumor samples are genotyped for EGFR mutations and ALK rearrangement. In addition, tumor samples are collected for research whole-exome or genome analysis to be conducted by the NCI. Patients without EGFR mutation or ALK fusion and not enrolled in ALCHEMIST therapeutic studies are followed for relapse and survival for 5 years. Attempts will be made to collect tumor samples from any biopsies performed at the time of recurrence to characterize clonal evolution that confirms metastatic potential.

ALCHEMIST-EGFR (A081105) is a randomized placebo-controlled trial of adjuvant erlotinib in patients with completely resected EGFR-mutant NSCLC following standard therapy. Similarly, ALCHEMIST-ALK (E4512) is a randomized placebo-controlled trial of adjuvant crizotinib in patients with completely resected ALK-positive NSCLC following standard therapy.
Background Rationale

ALCHEMIST-EGFR (A081105)

Of the components to this adjuvant program, the EGFR trial was the first to be conceived as EGFR kinase inhibitors have been a component of NSCLC treatment now for so many years. The recognition that the most dramatic responses with EGFR TKIs are best observed in patients whose tumors demonstrate EGFR tyrosine kinase (TK) mutations rather than EGFR overexpression, would rank among the most significant developments in lung cancer over the past three decades (16). EGFR TKIs administered to this subset of patients with metastatic disease as monotherapy produce a 2- to 3-fold increase in the response rates and progression-free survival compared with conventional chemotherapy. When erlotinib, an EGFR TKI, was administered following four cycles of platinum-based doublet therapy in the maintenance setting in patients with incurable advanced NSCLC, a striking improvement in progression-free survival (PFS) was observed in patients with EGFR TK mutations (PFS, HR, 0.10; 95% CI, 0.04–0.25, P < 0.0001; ref. 17).

However, for patients with earlier-stage disease the data are not well defined. The NCI-Canada (NCI-C) BR-19 study showed no improvement in OS with gefitinib in molecularly unselected patients with completely resected NSCLC (the primary objective of the study) when compared with patients receiving the placebo (18). Also, no improvement in OS was found in the subset of patients with EGFR TK mutation–NSCLC being treated with postoperative gefitinib, possibly due to the small numbers of patients with EGFR TK mutations and the brief duration of drug exposure (median duration of exposure was 5 months). A prospective study comparing erlotinib with placebo (RADIANT) in patients with resected NSCLC positive for EGFR expression by IHC or FISH did not show an improvement in OS (19). Unlike the ALCHEMIST trials, the RADIANT study was not restricted to those with EGFR TK mutations. The median disease-free survival was 48.2 months with placebo and 50.5 months with erlotinib (HR, 0.90, P = 0.3235). Of 973 patients, only a small number of patients (n = 161) had EGFR mutations. Though the median PFS in that subset of patients was superior with erlotinib (46.4 months) compared with placebo (28.5 months), these results were not statistically significant. Even though several studies have been conducted in patients with advanced NSCLC who harbor EGFR TK mutations, no large prospective randomized placebo-controlled adjuvant therapy trial with an EGFR TKI has been performed in patients with resected NSCLC whose tumor cells have mutated EGFR TK.

ALCHEMIST-ALK (E4512)

The presence of the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4–ALK) fusion gene plays an important role in a subset of patients with lung adenocarcinoma. An inhibitor of the ALK fusion kinase, crizotinib, has been shown to be superior to first- and second-line chemotherapy in patients with advanced NSCLC who have progressive disease following platinum-based chemotherapy (20, 21). There is now increasing knowledge regarding the natural history of ALK-positive NSCLC. Shaw and colleagues reported recently that for ALK-positive tumors in patients with metastatic NSCLC, the response to EGFR TKIs was minimal, but the outcomes with chemotherapy were comparable with those in wild-type EGFR patients (22). The prognosis of patients with early-stage, ALK-positive disease also appears to be sub-optimal compared with those without this genotype. In a cohort of approximately 200 patients with resected NSCLC, the presence of the ALK fusion protein was associated with an adverse outcome (23). The fact that the HR for OS was 2.3 with ALK-positive disease compared with outcomes in ALK-positive NSCLC patients not treated with crizotinib following surgical resection makes this a potential therapeutic option. No prospective studies have been done in the postoperative setting with crizotinib in patients with ALK-positive NSCLC.

ALCHEMIST screening trial (A151216)

In the setting of these parallel clinical trials studying resected NSCLC in rare molecularly defined subsets of patients, it was determined that a central protocol infrastructure would be invaluable for identification of potentially eligible patients and for central screening for appropriate genotypes. Furthermore, in the process of collecting tumor tissue for clinical genotyping, additional tumor tissue could be collected for genomic discovery efforts. Such advanced genomic analysis, performed on a clinically uniform and well-characterized NSCLC population, could allow for new insights into the relationship between tumor biology and clinical outcomes. The aims would be simple, to allow for accrual to the adjuvant treatment studies, while also allowing collection of research-grade tumor tissue for clinically relevant genomic discovery. In this way, the ALCHEMIST-screening protocol was developed not only to support the clinical success of the treatment trials but also to allow for a variety of correlative investigations.

Design and Statistical Considerations

ALCHEMIST screening trial

The primary objective of the ALCHEMIST screening trial is to centrally genotype resected nonsquamous NSCLC for EGFR mutations and ALK rearrangements to facilitate accrual to randomized adjuvant studies. Genotyping is being performed at Response Genetics, Inc. using direct sequencing of EGFR and ALK break-apart FISH. While genotyping may be performed in advance at a local laboratory, all cases must be confirmed centrally. In addition, all patients enrolled in ALCHEMIST are required to submit tumor tissue and a blood specimen to the NCI Center for Cancer Genomics (CCG) for research genomics. Unlike TCGA, ALCHEMIST is using formalin-fixed paraffin embedded (FFPE) tissue material for research genomics. The ALCHEMIST program encourages investigators to submit tumor blocks for genotyping (Response Genetics) and genomic analyses (CCG). Alternatively, tissue "scrolls" (10-micron thick) cut from the block can be sent for genotyping and genomic analyses because standard slides (5–7µm thick) yield poor-quality nucleic acids for genomic analyses. Blood is collected in EDTA and used for collection of matched germline DNA.

It is estimated that up to 8,000 patients may need to be genotyped for full accrual to the ALCHEMIST-EGFR (estimated prevalence 15% based on the advanced disease setting) and ALCHEMIST-ALK (estimated prevalence 5% based on the advanced-disease setting) studies. The primary endpoint of the ALCHEMIST screening trial is to perform central clinical genotyping to facilitate accrual to the adjuvant Intergroup studies, E4512 and A081105, as measured by rate of accrual, and to assess the feasibility of research-grade FFPE tissue collection for CCG analyses.
analysis, as measured by adequate specimens collected per month. The target accrual rate is around 16 patients per month for patients with EGFR mutations, exon 19 deletions, and L858 R only (A081105), and those with ALK rearrangements (E4512) to allow completion of enrollment within a 4-year period. See Fig. 1 for the ALCHEMIST schema.

The ALCHEMIST trial will also monitor the rate of agreement between the local and central testing for EGFR and ALK for the postoperative cohort when local test results are available. Specifically, each locally deemed EGFR-mutant or wild-type patient will also be classified by central assessment. Similarly, each patient deemed locally as ALK-rearranged or not by FISH will be classified by the central assessment. For each locally used assay, agreement will be defined as the proportion of patients deemed mutant (or wild-type) by local and central assessment divided by the number of evaluable patients, where an evaluable patient is defined as one who has a local assessment result and for whom tissue has been submitted for central assessment. An agreement rate of 90% or higher between the local assay and the central assessment will be deemed acceptable.

All patients enrolled in the ALCHEMIST screening trial will complete an epidemiologic questionnaire at registration and then

Figure 1.
Schema of the ALCHEMIST trials.
will be clinically followed for up to 5 years to collect details on time until recurrence and initial treatment at recurrence. For those patients undergoing a biopsy as part of the clinical care to confirm recurrence, a standard practice in most patients with recurrent NSCLC, optional tissue collection from the clinical biopsy will be sent to the NCI CCG for additional research genomics to understand genomic evolution. All of the genomic analyses will be performed at the CCG. Data generated from the genomic analyses will be shared with the research community in keeping with the established policies of the NCI.

ALCHEMIST-EGFR and ALCHEMIST-ALK adjuvant trials

The adjuvant trials are prospective, stratified, randomized double-blind phase III trials comparing personalized adjuvant treatment with a targeted agent versus placebo for 2 years in completely resected NSCLC stage IB–IIIA patients with EGFR mutation (ALCHEMIST-EGFR) or ALK-positive NSCLC (ALCHEMIST-ALK). The EGFR and ALK status are confirmed centrally through the ALCHEMIST trial, as outlined in Fig. 1. The primary analysis will include all patients who test positive for EGFR mutation or ALK rearrangement at the central reference laboratory (Response Genetics); however, patients with a local positive test but a negative central test (~5% of patients) will still be randomized onto the trials and will be included in a secondary analysis. Similar to the ALCHEMIST screening trial, continuous monitoring (after every 50 patients) of local versus central testing results will be performed within the adjuvant trials; if the discordant rate exceeds 15% within the first 100 patients, and exceeds 10% thereafter, the study team, NCI, and the FDA will take place to establish possible action plans.

The primary objective for the ALCHEMIST adjuvant trials is to assess whether positive stages IB–IIIA NSCLC treatment with erlotinib for EGFR-mutant or crizotinib for ALK following complete resection leads to longer OS than treatment with placebo alone. For the ALCHEMIST-EGFR trial, the target sample size is set so that there will be at least 85% power to demonstrate that erlotinib is superior to placebo with a HR of at least 0.67 in favor of erlotinib (50% improvement, or 7.5 years versus 5.0 years in median OS assuming exponential event times) using a one-sided type I error rate of 5%. The final analysis will take place once 183 deaths have occurred. The target accrual is 410 patients, with centrally confirmed EGFR mutation status and a projected accrual rate of 8 to 10 eligible patients per month (or 100 patients a year). Assuming a 5% rate of patient withdrawal/refusal, and a 5% rate for nonconfirmation of EGFR mutation by central testing, the total accrual is 450. For the ALCHEMIST-ALK trial, 360 patients will be accrued and randomized equally, for a total accrual of 180 patients per arm. Using an overall one-sided 0.05 level log-rank test, this study will have 80% power to detect a 33% reduction in the OS HR 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 on placebo alone to 99 months on crizotinib. The number of OS events needed to achieve this power is 164 events under the alternative hypothesis.

Several issues deserve further attention in the design of these adjuvant trials: specifically, the choice of the primary endpoint, the preliminary data used for the sample size determination, and the design parameters used. First, regarding the choice of endpoint, we believe that OS remains the most pertinent endpoint in the adjuvant setting for patients with curable disease. OS as an endpoint is unambiguous and can assess the true benefit of a new treatment relative to the current standard of care. The concern with OS as the endpoint, however, is that its effect can be diluted from crossover and effective subsequent therapies; however, if the therapies are purported to be equally effective in both arms the impact on absolute OS benefit would be minimal. In other words, if patients who receive placebo in the adjuvant setting derive substantial benefit from targeted therapies at the time of recurrence and earlier use of these agents in the postoperative setting does not increase the cure rates, there is no rationale for using targeted therapies in the adjuvant setting. Second, the choice of the OS estimates for the control arm for the sample size calculations is based on several assumptions. Although there are historical data on the standard-of-care arm for adjuvant trials, there are no historical data on the control arm for the EGFR- and ALK-positive NSCLC. The assumption therefore is that the outcome for the patients with EGFR mutant or ALK-positive NSCLC receiving standard-of-care treatment would be similar to that of the unselected population enrolled in historical trials. However, it is likely that these patients might have a different (worse or better) prognosis with standard of care. Finally, the choice of the statistical parameters, specifically, type I error rate for the two adjuvant trials, is higher than the standard accepted rate of two-sided 0.05 level. However, given the low prevalence of the EGFR- and ALK-positive patient populations, a one-sided type I error rate of 0.05 and power of 80% to 85% is justifiable for the sample size calculations for the two adjuvant trials in these rare patient populations.

Strategies for enrollment

Approximately 20% of patients with NSCLC present with potentially resectable disease. It is expected that 15% of these patients may have EGFR-mutant or ALK-positive NSCLC, accounting for roughly 3% of patients with newly diagnosed NSCLC in the United States annually. The clinical trial participation rate has been consistently under 5% in adults with cancer in this country. While these numbers are quite discouraging, a coordinated national effort will be made to recruit patients from academic and community centers. ALCHEMIST teams will be formed regionally to enhance trial accrual. These multidisciplinary teams will consist of surgeons, medical oncologists, clinical research associates, and patient advocates. ALCHEMIST teams will work closely with individual sites to encourage screening and enrollment. Periodic site visits, telephone conference calls, and educational meetings will be conducted regionally to promote the study. A slide kit, educational video, and pamphlets will be developed to educate physicians and patients about ALCHEMIST trials.

Impact of ALCHEMIST. Unlike some ongoing studies in Asia that are evaluating the superiority of EGFR TKIs in patients with resected NSCLC compared with cytotoxic chemotherapy (e.g., NCT02448797, NCT01405079), the ALCHEMIST trial is the only prospective randomized double-blind placebo-controlled trial to investigate the benefit of addition of molecularly targeted agents after standard postoperative chemotherapy in patients with resected NSCLC.

If the proposed therapeutic studies meet their primary endpoints, the standard of care for adjuvant therapy would change considerably. Erlotinib in patients with EGFR-mutant NSCLC and/or crizotinib in ALK-positive NSCLC would then become an
important addition to the standard of care for patients with resected NSCLC. This trial could provide the impetus to study novel molecularly targeted agents early in the drug development process. This study would provide the infrastructure for integration of either targeted novel therapies for a molecularly defined subset of patients or immunotherapies early in the drug development process and early in the disease process, significantly enhancing the prospect of cure. ALCHEMIST-Immunotherapy (EA5142) is a proposed amendment to ALCHEMIST that will randomize patients with completely resected EGFR and ALK wild-type tumors to nivolumab versus standard observation following standard therapy. A comprehensive survey of all dysregulated pathways that coexist alongside and/or complement standard therapy. This study would provide the infrastructure for integration of either targeted novel therapies for a molecularly defined subset of patients or immunotherapies early in the drug development process and early in the disease process, significantly enhancing the prospect of cure.

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