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

Ramaswamy Govindan, Washington University
Sumithra J. Mandrekar, Mayo Clinic
David E. Gerber, University of Texas Southwestern Medical Center
Geoffrey R. Oxnard, Harvard University
Suzanne E. Dahlberg, Harvard University
Jamie Chaft, Memorial Sloan-Kettering Cancer Center
Shakun Malik, National Cancer Institute
Margaret Mooney, National Cancer Institute
Jeffrey S. Abrams, National Cancer Institute
Pasi A. Jänne, Harvard University

Only first 10 authors above; see publication for full author list.

Journal Title: Clinical Cancer Research
Volume: Volume 21, Number 24
Publisher: American Association for Cancer Research | 2015-12-15, Pages 5439-5444
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1158/1078-0432.CCR-15-0354
Permanent URL: https://pid.emory.edu/ark:/25593/rvtr0

Final published version: http://dx.doi.org/10.1158/1078-0432.CCR-15-0354

Copyright information:
© 2015 American Association for Cancer Research.

Accessed September 6, 2017 7:35 PM EDT
ALCHEMIST Trials: A Golden Opportunity to Transform Outcomes in Early Stage Non–Small Cell Lung Cancer

Ramaswamy Govindan1, Sumithra J. Mandrekar2, David E. Gerber3, Geoffrey R. Oxnard4, Suzanne E. Dahlberg5, Shakun Malik6, Margaret Mooney6, Jeffrey S. Abrams6, Pasi A. Jänne7, David R. Gandara8, Suresh S. Ramalingam9, and Everett E. Vokes10,11

1 Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 2 Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota 3 Division of Hematology and Oncology, UT Southwestern Medical Center, Dallas, Texas 4 Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 5 Department of Biostatistics and Computational Biology, Harvard School of Public Health, Dana-Farber Cancer Institute, Boston, Massachusetts 6 Clinical Investigations Branch, Cancer Therapy Evaluation Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 7 Lowe Center for Thoracic Oncology and Belfer Institute for Applied Cancer Science, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 8 Division of Hematology and Oncology, UC Davis Comprehensive Cancer Center, Sacramento, California 9 Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, Georgia 10 Department of Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, Illinois 11 The University of Chicago Comprehensive Cancer Research Center, Chicago, Illinois

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 (TCGA) project to understand the complexities of the genomic landscape of lung cancer will be supplemented further by studying a large number of tumor specimens. Adjuvant Lung Cancer Enrichment Marker

Corresponding Author: Ramaswamy Govindan, Division of Medical Oncology, Washington University School of Medicine, 660 S. Euclid, Box 8056, St. Louis, MO 63021. Phone: 314-362-5737; Fax: 314-362-4232; rgovinda@dom.wustl.edu.

R. Govindan and E.E. Vokes share senior authorship.

Disclosure of Potential Conflicts of Interest

R. Govindan is a consultant/advisory board member for AbbVie, Boehringer Ingelheim, Celgene, Clovis Oncology, Genentech, GlaxoSmithKline, Helsinn, Merck, and Pfizer. D.E. Gerber reports receiving a commercial research grant from Genentech. G.R. Oxnard is a consultant/advisory board member for AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Genentech, Novartis, and Sysmex. P.A. Jänne reports receiving commercial research support from Astellas Pharma and AstraZeneca; has ownership interest (including patents) in Gatekeeper Pharmaceuticals; and is a consultant/advisory board member for AstraZeneca, Chugai Pharma, Pfizer, and Roche. D.R. Gandara is a consultant/advisory board member for Genentech. S.S. Ramalingam is a consultant/advisory board member for AstraZeneca, Boehringer Ingelheim, Bristol-Myer Squibb, Celgene, Eli Lilly, and Genentech. No potential conflicts of interest were disclosed by the other authors.
Identification and Sequencing Trial (ALCHEMIST) is a National Cancer Institute (NCI) sponsored national clinical trials network (NCTN) 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 if 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 vs. 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 and 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.

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 histological subtype of non-small cell lung cancer (NSCLC) (2). Advent of targeted therapies, specifically those directed towards epidermal growth factor receptor (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%-15% in patients with stage I-III NSCLC (7-9). The data from LACE meta-analysis confirmed a 5.4% overall survival (OS) benefit at 5 years with adjuvant chemotherapy compared to observation (HR=0.89, 95% CI=0.82-0.96) (10). However most of the benefit seems to be restricted to patients with stage II and III NSCLC. Adjuvant post-operative chemotherapy has become a standard of care in patients with resected stage II to III NSCLC. Despite the use of post-operative chemotherapy, nearly a third of patients with stage I NSCLC and at least 30%-50% of patients with stage II and III NSCLC will still die from recurrent disease. There is thus a significant need to improve the outcomes in these patients.

It has become apparent in the 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 patients based on the tumor genotype following surgical
resection in order to cure more patients with lung cancer. Molecularly targeted therapies have not yet been shown to improve overall survival in patients in this setting. Ongoing studies in Asia are evaluating the superiority of EGFR TK inhibitors in patients with resected NSCLC compared to cytotoxic chemotherapy (for example, NCT02448797, NCT01405079). The NCTN mechanism is uniquely suited to address this issue by facilitating genomic screening nationally that will allow serial investigation of a number of new compounds in clearly defined subsets of patients with resected NSCLC.

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 in order 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 in order 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 National Cancer Institute (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 non-squamous NSCLC in trials of genotype-directed adjuvant therapy. The choice of non-squamous 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 five years. Attempts will be made to collect tumor samples from any biopsies performed at the time of recurrence to characterize clonal evolution that confers 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 TK inhibitors are best observed in patients, whose tumors demonstrate *EGFR* TK mutations rather than *EGFR* over expression, would rank among the most significant developments in lung cancer over the past three decades (16). EGFR TK inhibitors administered to this subset of patients with metastatic disease as monotherapy produce a two to three-fold increase in the response rates and progression free survival compared to conventional chemotherapy. When erlotinib, an EGFR TK inhibitor, was administered following four cycles of platinum based doublet therapy in the maintenance setting in patients with incurable advanced NSCLC, there was a striking improvement in the progression free survival in patients with *EGFR* TK mutations (PFS, HR 0.10, 95% CI: 0.04-0.25, p<0.0001) (17).

However, for patients with earlier stage disease the data are not well defined. The results of the National Cancer Institute - Canada (NCI-C) BR-19 study showed no improvement in overall survival with gefitinib in molecularly unselected patients with completely resected NSCLC (the primary objective of the study) when compared with placebo (18). There was also no improvement in overall survival in the subset of patients with *EGFR* TK mutation NSCLC with post-operative 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 overall survival (19). Unlike the ALCHEMIST, the RADIANT study was not restricted to those with *EGFR* TK mutation. 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 progression free survival in that subset of patients was superior with erlotinib (46.4 months) compared to 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 TK inhibitor has been performed in patients with resected NSCLC whose tumors cells have mutated *EGFR* TK.

**ALCHEMIST-ALK (E4512)**

The presence of 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 tyrosine kinase inhibitors was minimal, but the outcomes with chemotherapy were comparable to that in wild-type EGFR patients (22). The prognosis of patients with early stage, ALK positive patients also appears to be sub-optimal compared to those without this genotype. In a cohort of approximately 200 patients with resected NSCLC, the presence of ALK fusion protein was associated with an adverse outcome (23). The hazard ratio for overall survival was 2.3 with ALK positive disease compared to those without the use of crizotinib in patients with ALK positive NSCLC following surgical resection is a potential therapeutic option. No prospective studies have been done in the post-operative 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 the 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 characterize NSCLC population, could allow for new insights into the relationship between tumor biology and clinical outcome. 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 both to support the clinical success of the treatment trials while also allowing 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 non-squamous 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. Additionally, 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. 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 since standard slides (5 micron 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 8000 patients may need to be genotyped in order to fully accrue 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 analysis, as measured by adequate specimens collected per month. The target accrual rate is around 16 patients per month both for patients with EGFR mutations – exon 19 deletions and L858 R only (A081105) and those with ALK rearrangements (E4512) so as to allow completion of enrollment within a four-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 post-op 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 one who has a local assessment result and has submitted tissue 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 into ALCHEMIST screening trial will complete an epidemiological questionnaire at registration and then 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 in order to understand genomic evolution. All of the genomic analyses will be performed at the Center for Cancer Genomics of the NCI. Data generated from the genomic analyses will be shared with the research community consistent 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 two 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 or ALK at the central reference lab (Response Genetics); however patients with a local positive test but 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, discussions between the study team, NCI, and the FDA will take place to discuss possible action plans.

The primary objective for the ALCHEMIST adjuvant trials is to assess whether completely resected NSCLC stage IB-IIIA patients with an EGFR or ALK mutation treated with erlotinib for EGFR mutant or crizotinib for ALK mutant following complete resection have longer overall survival (OS) than patients treated 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 hazard ratio (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 are observed. The target accrual is 410 patients, with centrally confirmed EGFR mutation status, with a projected accrual rate of 8-10 eligible patients per month (or 100 patients a year). Assuming a 5% rate of patient withdrawal/refusal, and a 5% rate for non-confirmation of EGFR 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 hazard rate 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 end point 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 cross over 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 post-operative 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. While 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 mutant population. The assumption therefore is that the outcome for the patients with EGFR or ALK mutation receiving standard of care would be similar to that of the unselected population enrolled in historical trials. It is however 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 standardly accepted rate of 2-sided 0.05 level. However, given the low prevalence of the EGFR and ALK positive patient populations, a 1-sided type I error rate of 0.05 and power of 80-85%
are 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 of ongoing studies in Asia that are evaluating the superiority of EGFR TK inhibitors in patients with resected NSCLC compared to cytotoxic chemotherapy (for example, NCT02448797, NCT01405079), ALCHEMIST trial is the only prospective randomized double-blind placebo controlled trial to investigate the benefit of addition of molecularly targeted agents following standard post operative 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 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 *EGFR* TK mutations and ALK rearrangement could potentially shed more light on the mechanisms of intrinsic and acquired resistance beyond what is known already. In addition, this study will be the first opportunity to systematically characterize the presence of other molecular changes, more specifically, changes in the broader class of cell signaling kinases that could potentially affect the outcomes in response to specific targeted therapies using rapidly emerging high throughput technologies.
Acknowledgments

Grant Support

This work was supported in part by the NCI of the NIH under award numbers U10CA180821 and U10CA18088 (to Alliance for Clinical Trials in Oncology) and CA180820, CA180794, CA180870, and CA180864 (to S.E. Dahlberg).

References


Figure 1.
Schema of the ALCHEMIST Trials