Designing a definitive trial for adjuvant targeted therapy in genotype defined lung cancer: the ALCHEMIST trials

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Abstract: Genotype-directed targeted therapies have revolutionized the treatment of metastatic non-small cell lung cancer (NSCLC) but they have not yet been comprehensively studied in the adjuvant setting. Previous trials of adjuvant targeted therapy in unselected early stage NSCLC patients showed no benefit versus placebo, however retrospective data suggests improved disease free survival (DFS) with epidermal growth factor receptor (EGFR) inhibitors in patients with appropriate molecular alterations. A definitive prospective, randomized, placebo-controlled trial of targeted therapies for NSCLC is needed to determine the efficacy of targeted therapy following surgical resection and standard adjuvant therapy. The principal challenges facing such a trial are (I) identification of actionable alterations in early stage patients; and (II) realization of sufficient enrollment to power definitive analyses. The ALCHEMIST trial (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) was designed to overcome these challenges. Using the national clinical trials network (NCTN) of the National Cancer Institute (NCI), several thousand patients with operable NSCLC will undergo tumor genotyping for *EGFR* mutations or rearrangement of anaplastic lymphoma kinase (*ALK*). Following resection and completion of standard adjuvant therapy, patients with *EGFR*-mutant NSCLC will be randomized to erlotinib versus placebo (1:1), those with *ALK*-rearranged NSCLC will be randomized to crizotinib versus placebo (1:1), while those not enrolled onto the adjuvant trials will continue to be followed on the screening trial. ALCHEMIST also provides for the collection of tissue at baseline and at recurrence (if available) to characterize mechanisms of recurrence and of resistance to targeted therapy. Thus, ALCHEMIST is a platform for validation of targeted therapy as part of curative care in NSCLC and creates an opportunity to advance our understanding of disease biology.

Keywords: Clinical trial design; targeted therapy; adjuvant therapy; non-small cell lung cancer (NSCLC)

Introduction

Targeted therapies, specifically tyrosine kinase inhibitors (TKIs), have redefined the standard of care for metastatic epidermal growth factor receptor (*EGFR*)-mutant or anaplastic lymphoma kinase (*ALK*)-rearranged non-small cell lung cancer (NSCLC) (1-8). The success of these agents exemplifies the current trend toward rationally designed compounds which target specific molecular alterations in cancer. The benefit associated with these agents is similar to the transformative benefit seen with imatinib in gastrointestinal stromal tumor (GIST) or with tamoxifen or trastuzumab for metastatic breast cancers (9-16). But while imatinib, tamoxifen and trastuzumab have long been employed in the adjuvant setting, targeted therapies have not been comprehensively studied in early stage NSCLC (*Tables 1,2*) (17-20,25-28). About half of all patients who present with potentially curable NSCLC will die from recurrent disease within 5 years (29). By comparison, 5-year survival among 200 patients with high-risk early stage KIT positive GIST treated with imatinib following surgery was 92% (18) and 5-year survival in operable ER positive or

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Table 1 Studies of adjuvant targeted therapies in diseases other than lung cancer

Trial	Disease	Treatment	Exposure	Primary endpoint	DFS	OS
Dematteo et al. (17)	KIT+ GIST, >3 cm	Imatinib vs. placebo (1:1)	1 year	DFS	HR 0.35 (95% CI: 0.22-0.53) P<0.0001; at 1 year, 98% vs. 83%	HR 0.66 (0.22-2.03) P=0.47; at 4 years, 99% vs. 98%
Joensuu et al. (18)	KIT+ GIST, high-risk	1 year vs. 3 years imatinib (1:1)	1 year vs. 3 years	DFS	HR 0.46 (0.32-0.65) P<0.001; at 5 years, 66% vs. 48%	HR 0.45 (0.22-0.89) P=0.02; at 5 years, 92% vs. 81.7%
IBCSG trial 13-93 (19)	ER+ breast cancer, node+	Tamoxifen vs. observation (1:1)	5 years	DFS	HR 0.59 (0.46-0.75) P<0.0001; at 5 years, 75% vs. 62%	HR 0.86 (0.62-1.19) P=0.36; at 5 years, 87% vs. 87%
HERA trial (20)	HER2+ breast cancer	Trastuzumab vs. observation (1:1)	1 year	DFS	HR 0.54 (0.43-0.67) P<0.0001; at 2 years, 86% vs. 77%	HR 0.76 (0.47-1.23) P=0.26; at 2 years, 96% vs. 95%

DFS, disease free survival; OS, overall survival; GIST, gastrointestinal stromal tumor; HR, hazard ratio; CI, confidence interval.

Table 2 Prior studies of adjuvant targeted therapies in NSCLC

Trial	Disease	Treatment	Exposure	Primary endpoint	DFS	OS
NCIC CTG BR.19 trial (21)	NSCLC, no molecular selection	Gefitinib vs. placebo (1:1)	2 years	OS	HR 1.22 (0.93-1.61) P=0.15; median 4.2 years vs. NR; at 6.3 years, 52% vs. 59%	HR 1.24 (0.94-1.64) P=0.14; median 5.1 years vs. NR; at 6.3 years, 54% vs. 59%
RADIANT trial (22)	NSCLC, EGFR+ by IHC or FISH	Erlotinib vs. placebo (2:1)	2 years	DFS	HR 0.90 (0.74-1.10) P=0.3235; median 50.5 months vs. 48.2 months	HR 1.13 (0.88-1.45) P=0.3350
D'Angelo et al. (23)	NSCLC, EGFR mutant (retrospective analysis)	Erlotinib or gefitinib [84] vs. no adjuvant TKI [202]	Median 18.6 months (0.1-51.4)	Retrospective	HR 0.43 (0.26-0.72) P=0.001	HR 0.50 (0.23-1.08) P=0.076
SELECT trial (24)	NSCLC, EGFR mutant	Erlotinib	2 years	DFS	90% at 2 years	92% at 2 years

NSCLC, non-small cell lung cancer; DFS, disease free survival; OS, overall survival; HR, hazard ratio; NR, not reached; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

HER2 positive breast cancers treated with tamoxifen or trastuzumab is 92% (25) and 91% (26,27) respectively. It is fitting to now aim to transform adjuvant therapy of NSCLC through incorporation of targeted agents just as it has been transformed for these other diseases, but to achieve this a prospective controlled trial in a carefully selected population is needed.

Definitive study of adjuvant targeted therapy in NSCLC faces challenges. Such a trial must establish a system to prospectively identify patients with actionable genetic alterations and allocate them appropriately, as targeted therapy does not improve outcomes in unselected populations of early stage NSCLC (*Table 2*) (21,22). Furthermore, a successful trial must overcome the consistently low participation rate (<5%) in clinical trials among adults with cancer in the United States (30). The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) combines the

Table 3 ALCHEMIST trials

Trial	Disease	Treatment	Exposure	Primary endpoint	DFS	OS
ALCHEMIST EGFR	NSCLC, EGFR mutant	Erlotinib *vs.* placebo (1:1)	2 years	OS	NR	Goal HR 0.67; median 7.5 *vs.* 5.0 years
ALCHEMIST ALK	NSCLC, ALK rearranged	Crizotinib *vs.* placebo (1:1)	2 years	OS	NR	Goal HR 0.67; median 7.5 *vs.* 5.0 years

DFS, disease free survival; OS, overall survival; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NR, not reached; HR, hazard ratio; ALK, anaplastic lymphoma kinase.
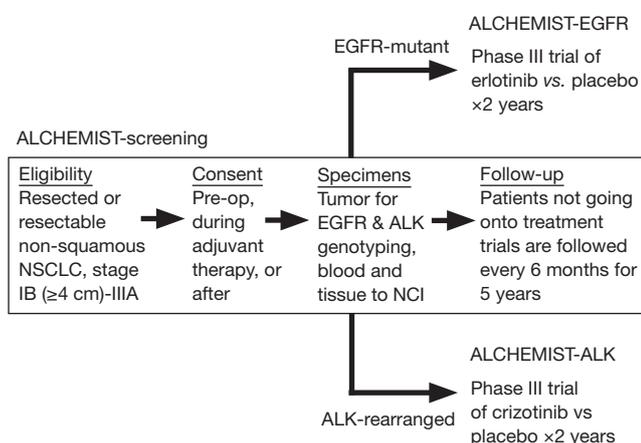
Figure 1 Schema for the three current ALCHEMIST trials.

resources of the National Cancer Institute (NCI) with the broad reach of the NCTN to overcome these challenges. The NCTN, built from the previous cooperative group system, will use its academic and community centers to identify eligible patients who will agree to have tumor genotyping performed. The NCI's Center for Cancer Genetics (CCG) will perform further genomic analysis of all samples. The ALCHEMIST design will allow comprehensive investigation of targeted therapies in resected NSCLC, and will be a platform that can grow with future therapeutic advances (*Table 3*).

Design overview

ALCHEMIST is designed to facilitate prospective screening, identification and enrollment of high-risk early stage (IB-IIIA), genotype-selected NSCLC patients in randomized trials of targeted therapy. ALCHEMIST currently consists of three integrated protocols: a screening study (A151216, coordinated by the Alliance for Clinical Trials in Oncology, PI: Geoffrey Oxnard) and two treatment trials (A081105, coordinated by the Alliance for Clinical Trials in Oncology, PI: Ramaswamy Govindan; E4512, coordinated by the ECOG-ACRIN Cancer Research Group, PI: David Gerber). Additional protocols may be included as other compelling therapies, such as immunotherapy agents, emerge.

All patients must first consent to ALCHEMIST Screening (A151216) to be considered for ALCHEMIST trials of targeted therapy (*Figure 1*). Patients can consent prior to surgery or after resection. Eligible patients must have completely resected non-squamous NSCLC. Tumor specimens will be tested centrally for *EGFR* kinase domain mutations using sequencing, and for *ALK* rearrangements using FISH; patients must undergo confirmatory central genotyping on study regardless of whether any local genotyping was positive or negative for *EGFR* or *ALK*. Remaining tumor tissue will be paired with blood specimens for exploratory genomic analysis by the NCI. Patients whose tumors are found to harbor *EGFR* mutation or *ALK* rearrangement will be offered enrollment onto trials of adjuvant targeted therapy. Patients not enrolled onto the adjuvant trials will be followed on ALCHEMIST screening every 6 months for 5 years. In order to advance the understanding of genomic and biological mechanisms of recurrent or resistant disease, tumor samples from any biopsies performed at the time of recurrence will be collected and studied. While it is understood that not all patients will have tissue available at recurrence for genomic analysis, it is expected that a subset of patients will undergo resection or metastectomy as part of their clinical care and therefore will have a larger specimen available for study.

The flow of biospecimens and clinical data on ALCHEMIST are described in *Figure 2*. All biospecimens are logged and tracked through BioMS, and all genotype and clinical data are collected in Medidata Rave. While

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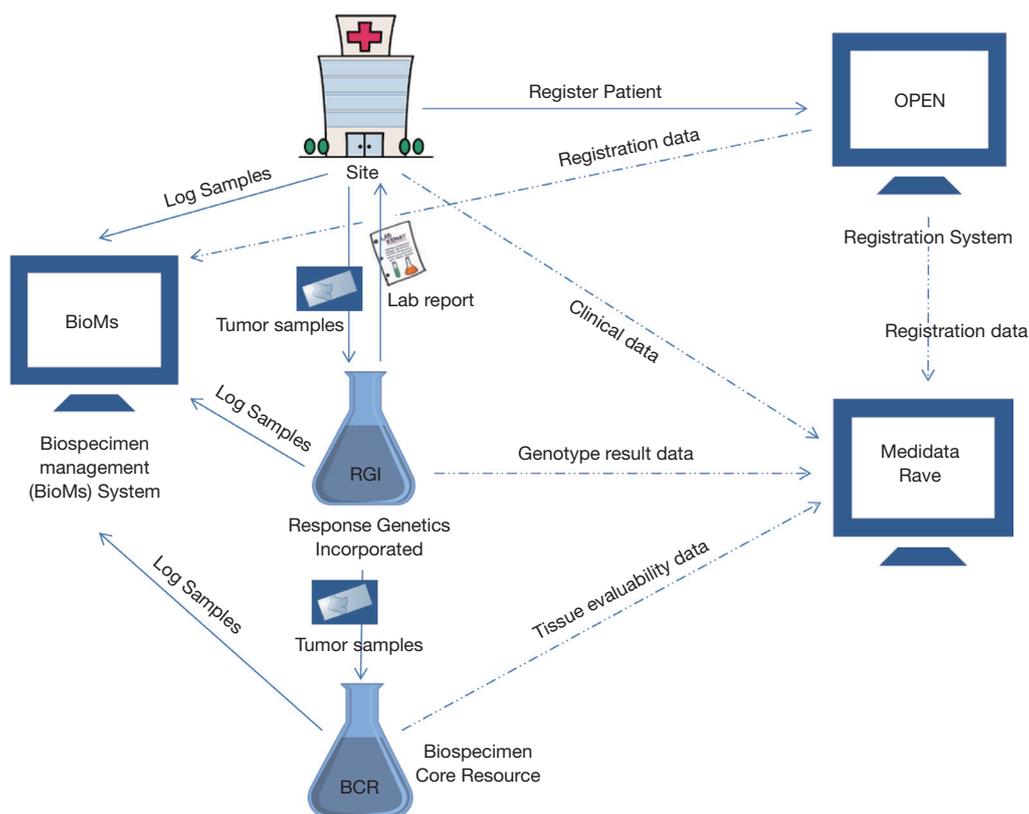
Figure 2 Systems for biospecimen and data flow for ALCHEMIST-Screening trial.

there were some existing integrations between the patient registration system (OPEN) and Medidata Rave, infrastructure to interface with laboratory partners (RGI, BCR) and Medidata Rave were built specifically for ALCHEMIST. As noted above and in *Figure 2*, beyond the predefined molecular alterations to identify potential patients for the EGFR and ALK sub-studies, full genomic characterization of submitted tissue will occur at the NCI-CCG. Regular conference calls and data exchanges between the different entities involved in ALCHEMIST ensure smooth functioning of this complex infrastructure.

Following standard adjuvant therapy, patients with fully resected *EGFR*-mutant NSCLC will be randomized to erlotinib versus placebo (1:1) for two years under ALCHEMIST-EGFR (A081105). Similarly, patients with fully resected *ALK*-rearranged NSCLC will be randomized to crizotinib *vs.* placebo (1:1) for two years under ALCHEMIST-ALK (E4512) following standard adjuvant therapy. As erlotinib and crizotinib are well established standard therapies for advanced NSCLC, it is anticipated that toxicity and compliance will be manageable throughout

the NCTN.

The primary endpoint for ALCHEMIST adjuvant therapeutic trials is overall survival (OS). For the *EGFR* trial (A081105), a total accrual of 450 patients will allow for a 5% rate of study withdrawal and 5% non-confirmation rate of *EGFR* mutation via central testing, leaving the target accrual of 410 patients to power definitive analysis of the primary endpoint. This sample size will provide at least 85% power to show a hazard ratio (HR) of 0.67 or better in favor of erlotinib over placebo after 183 events, using a one-sided type I error of 5%. There is one planned interim analysis for futility when 50% of the events have been observed, using the O'Brien-Fleming stopping boundary. If the observed HR is greater than or equal to 0.96 (P value is 0.43 or greater), the recommendation will be to stop further accrual (if the trial is still accruing). It is expected that this trial will complete its targeted accrual. For the *ALK* trial (E4512), a total accrual of 378 patients will allow for a 5% non-confirmation rate of *ALK* rearrangement via central testing, leaving the target accrual of 360 patients to power definitive analysis of OS. This sample size will provide at

least 80% power to detect a HR of 0.67 or better in favor of crizotinib over placebo after 164 events, using a one-sided type I error of 5%. A continuous efficacy-monitoring plan based on the O'Brien-Fleming group sequential boundary for the sequential testing incorporating the Lan and DeMets methodology for the error spending rate function is proposed: 10 planned interim analyses for OS starting at roughly 25% information (42 events under the alternative hypothesis) and one final analysis. At each interim analysis for efficacy, the study will also be monitored for early stopping in favor of the null hypothesis (i.e., futility) using repeated confidence interval methodology similar to that described by Jennison and Turnbull. At each interim analysis, if the nominal (1-2× alpha) confidence interval on the OS HR does not contain the target alternative of 0.67, then the data safety monitoring committee may consider terminating the study early for overall lack of treatment differences.

Rationale

EGFR TKIs are effective therapies, but must be employed in appropriately selected populations. OPTIMAL, a phase III randomized trial of erlotinib versus carboplatin and gemcitabine (1:1) for metastatic, previously untreated *EGFR*-mutant NSCLC demonstrated a significantly longer progression-free survival (PFS) for patients treated with erlotinib {13.1 [95% confidence interval (CI): 10.58-16.53] *vs.* 4.6 (4.21-5.42) months; HR: 0.16 (95% CI: 0.10-0.26); P<0.0001} (4). The IPASS trial further showed that clinical criteria alone are not sufficient to predict benefit from EGFR TKI—molecular analysis is needed (6,31). A total of 1,217 East Asian former light or non-smokers with treatment naïve advanced adenocarcinoma were randomized to gefitinib or carboplatin-paclitaxel (6). No advantage in OS was observed between the two arms [18.6 months, HR: 0.91 (95% CI: 0.76-1.10)] (31). While PFS (primary endpoint) was improved in the gefitinib arm [5.7 months, HR: 0.74 (95% CI: 0.65-0.85; P<0.001)], PFS benefit was limited to patients with *EGFR* mutations, as gefitinib was associated with shorter PFS for patients with wild-type *EGFR* [HR: 2.85 (95% CI: 2.05-3.98); P<0.001] (31).

No prospective, placebo controlled trial has examined adjuvant treatment with EGFR TKI in an appropriately selected population. The BR19 trial randomized patients with completely resected NSCLC to receive gefitinib or placebo for 2 years (21). The trial closed early due to lack

of benefit, enrolling 503 of 1,242 planned patients (21). There was no significant difference in OS (HR: 1.24; 95% CI: 0.94-1.64; P=0.14) or DFS (HR: 1.22; 95% CI: 0.93-1.61; P=0.15) between the two arms (*Table 2*) (21). However, patients were not selected based on *EGFR* mutation status, and only 15 patients were found to have *EGFR* activating mutations (21). The RADIANT trial selected for EGFR expression or amplification, not *EGFR* mutation, in patients with resected NSCLC and showed no improvement in OS for erlotinib *vs.* placebo (*Table 2*) (22,32). Median DFS was improved with erlotinib *vs.* placebo in 161 patients with *EGFR* mutations (46.4 *vs.* 28.5 months; HR: 0.61, 95% CI: 0.38-0.98, P=0.039), however, this result was not statistically significant due to the hierarchical testing procedure employed by the trial (22,32). Retrospective data from MSKCC suggests improved DFS (HR: 0.43, 95% CI: 0.26-0.72, P=0.001) and OS with adjuvant EGFR TKI in resected *EGFR*-mutant NSCLC, but OS figures are not significant (HR: 0.50, 95% CI: 0.23-1.08, P=0.076) (*Table 2*) (23).

Motivated by this retrospective data, the SELECT trial enrolled 100 *EGFR*-mutant NSCLC patients to prospectively test the efficacy and feasibility of adjuvant erlotinib in molecularly-selected patients (24,33). Median DFS and OS have not yet been reached, but the 2-year DFS observed by the trial was 90% (n=89) (*Table 2*) (24). Importantly, many patients underwent dose reduction, which allowed improved compliance for the duration of adjuvant therapy. Building off the feasibility demonstrated in the SELECT trial, ALCHEMIST-Screening (A151216) in conjunction with ALCHEMIST-EGFR (A081105) will identify patients with resected *EGFR*-mutant lung cancer for enrollment onto a randomized, placebo-controlled trial to power definitive analyses regarding efficacy of EGFR TKI in resected *EGFR*-mutant NSCLC.

Phase III trials have also confirmed the efficacy of targeted TKI therapy in advanced *ALK*-rearranged NSCLC, but no prospective studies have examined adjuvant TKI in early stage *ALK*+ patients (7,8). A randomized study of second-line crizotinib *vs.* pemetrexed or docetaxel for *ALK*+ locally advanced or metastatic NSCLC demonstrated a median PFS of 7.7 months for crizotinib *vs.* 3.0 months for chemotherapy (HR: 0.49, 95% CI: 0.37-0.64, P<0.001) (7). These findings, combined with recent data that point to poorer prognosis for early stage *ALK*+ patients (34), make crizotinib an attractive option for incorporation into

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curative therapy for these patients. ALCHEMIST-ALK (E4512) represents a definitive trial to evaluate adjuvant ALK TKI in this subpopulation of NSCLC.

Endpoints and design rationale

The primary objective of ALCHEMIST-Screening is to facilitate accrual to ALCHEMIST trials of targeted therapy. ALCHEMIST-Screening aims to genotype up to 8,000 high-risk early stage NSCLC patients in order to fully accrue ALCHEMIST-EGFR and ALCHEMIST-ALK, based on estimated 15% prevalence of *EGFR* kinase domain mutations and 5% prevalence of *ALK* rearrangements (7,35,36). The desired rate of accrual to the therapeutic randomized trials is 16 patients per month: ~10 patients for the ALCHEMIST-EGFR trial and ~6 per month for ALCHEMIST-ALK trial, in order to reach completion within four years.

OS was chosen as the primary endpoint for ALCHEMIST trials of targeted therapy because it represents the most significant endpoint for patients with curable disease. In this setting, OS is the best measure for absolute benefit of a new treatment relative to standard of care. OS as an endpoint can be diluted by the effect of subsequent therapies, but if the benefit afforded by targeted therapy in the adjuvant setting does not surpass the benefit of targeted therapy at recurrence for control arm patients, then the value of adjuvant targeted therapy is less clear compared to treatment at time of recurrence.

The type I error rate (1-sided 0.05) for the two adjuvant trials is higher than the standard rate (2-sided 0.05) to accommodate the low prevalence of *EGFR* kinase mutations and *ALK* rearrangements in NSCLC and make the studies feasible. OS estimates for placebo arms for the purpose of sample size calculations were based on historical data of standard of care outcomes from unselected early stage NSCLC. It is important to note that, while there is less historical data for the standard of care outcome in early stage *EGFR*-mutant or *ALK*-rearranged patients, there are indications that *EGFR*-mutant NSCLC may predict a better prognosis, while *ALK*-rearranged NSCLC may be associated with a poorer prognosis (23,34,36,37).

The rate of agreement between the local and central testing results for EGFR and ALK will be monitored within the ALCHEMIST screening trial. 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.

Conclusions

If the ALCHEMIST trials of targeted therapy reach their primary objectives, genotype-directed TKIs will become an important addition to standard curative therapy for early stage NSCLC patients with appropriate molecular alterations. The results of these trials may encourage further study of highly active targeted agents as part of curative therapy for NSCLC. For example, a trial studying adjuvant PD-1 inhibition is in development as part of the ALCHEMIST effort. Tissue collection and analysis through ALCHEMIST-Screening may also reveal new molecular targets, and may in turn pave the way for novel therapies to be studied in the adjuvant setting for appropriate populations.

Acknowledgements

Footnote

Conflicts of Interest: GR Oxnard has received consulting fees from Astra Zeneca and Boehringer Ingelheim and honoraria from Chugai.

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