Update #04
07/01/2017

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE FOR ALLIANCE A151216

Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST)
A screening trial for A081105, E4512 and EA5142

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[X]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[ ]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[ ]	Other		

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL

CTSU Contacts and Information Page (p. 3)
The information in the table has been updated with new CTSU language.

Section 4.2.3 CTSU Registration Procedures
This section has been updated based on the new CTSU template language.

Section 5.2 Blood Collection and Submission for All Patients
- In the first paragraph the instruction to keep the blood at room temperature prior to shipping has been included.
- In the second paragraph the shipment instructions have been updated.

Section 5.3 Tissue Preparation
In the last paragraph additional information about how to label the scroll and slide has been added, and a note about contacting the BCR for an airbill has been added.

Section 5.4 Specimen Submission using the Alliance Biospecimen Management System
The last sentence of the first paragraph has been changed to inform sites they "will" use BioMS to order kits, rather than they "may" use BioMS.

In the fourth paragraph instructions for labeling the specimens have been updated.

Section 5.4.2 Scrolls and H&E Slides Submission
The first sentence, referring to the kits, has been removed. This language is in Section 5.4.

Section 5.5 Tissue Submission at Progression
In the first paragraph information about storing the FFPE material at room temperature has been added. The third sentence, which includes instructions on how to label the materials, has been added.
In the second paragraph it has been clarified that the molecular report for the recurrence specimen should be submitted via RAVE.

UPDATES TO THE MODEL CONSENT:

What are the Possible Treatment Studies I Could be Offered Based on the Results of my Genetic Tests?
The reference to the placebo has been removed from the first and second bullet. In both the E4512 and A081105 trials patients will be randomized to drug vs observation instead of drug vs placebo.

A Replacement Protocol and Model Consent Document have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A151216

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

A screening trial for A081105, E4512 and EA5142

ClinicalTrials.gov Identifier: NCT02194738

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Update 03	01/15/17
Update 04	07/01/17

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org and select the Regulatory Submission sub-tab under the Regulatory tab.)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at: https://www.ctsu.org/OPEN_SYSTEM or https://OPEN.ctsu.org Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission schedule on the Alliance/CTSU websites for further information.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e., patient eligibility or treatment-related) contact the Study Chair of the Lead Protocol Organization.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org.		

Patient Pre-Registration Eligibility Criteria

- **For pre-surgical patients**: Suspected resectable NSCLC and suspected stage large IB (≥ 4 cm), II (IIA or IIB) or IIIA
- **For post-surgical patients:** Complete resection of NSCLC, path stage large IB (≥ 4 cm), II (IIA or IIB) or IIIA
- **For all patients:**

  ECOG Performance Status 0-1; Age ≥18 years

  No patients who have received neoadjuvant therapy (chemotherapy or radiotherapy)

  No locally advanced or metastatic cancer requiring systemic therapy within 5 years; no secondary primary lung cancer concurrent or within 2 years.

  No prior treatment with agents targeting EGFR mutation, ALK rearrangement or PD-1/PD-L1/CTLA-4

  Non-pregnant and non-lactating

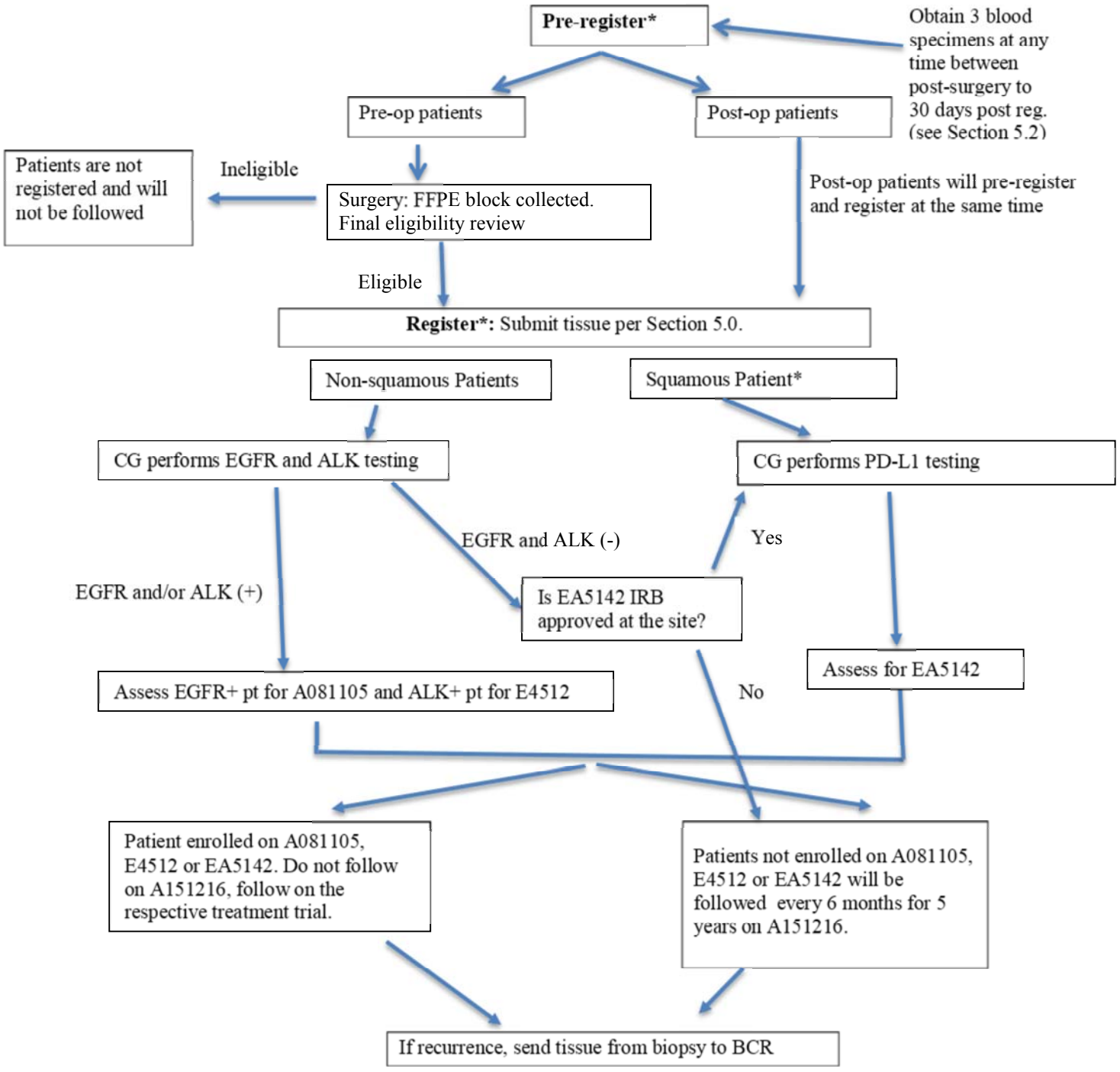
  Patients with local genotyping are eligible, regardless of the local result

  No recurrent lung cancer patients

Patient Registration Eligibility Criteria

- Completely resected stage large IB (≥4 cm), II (IIA or IIB) or IIIA non-squamous NSCLC. Squamous cell patients are eligible as long as the enrolling site has EA5142 IRB approved.
- Adequate tissue available for the required analyses (either clinical tissue block or slides and scrolls)
- Patients should be registered within specific timeframes, based on adjuvant chemo (see Section 3.2)

Schema



* Patients with squamous cell carcinoma are able to pre-register to A151216 only when the enrolling site has the EA5142 trial IRB approved.

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1.0 INTRODUCTION

1.1 Selecting Therapies Based Upon Lung Cancer Genotype

The management of advanced lung adenocarcinoma has been transformed by the identification of targetable genotypes in a significant proportion of patients. Genotyping advanced lung adenocarcinomas for *EGFR* mutations and *ALK* rearrangements is now a routine part of care, as these genotypes indicate unique sensitivity to treatment with tyrosine kinase inhibitors (TKIs) such as erlotinib and crizotinib (1,2). However, these highly active targeted therapies do not lead to cures – resistance invariably develops.

1.2 Adjuvant Targeted Therapies

To determine whether highly active TKIs can improve cure rates, they must be studied in earlier stage disease (I-III). EGFR TKIs like erlotinib and gefitinib have been studied in the adjuvant setting, but not in genotype-selected populations (3,4). For this reason, studies randomizing genotype-selected lung cancer populations to TKI or placebo are under development both for erlotinib and crizotinib. To make these studies feasible, large numbers of resected lung cancers will need to undergo screening for *EGFR* mutations and *ALK* rearrangements. Because genotyping of resected lung cancers is not a routine part of clinical care, a screening trial is needed to identify *EGFR*-mutant and *ALK*-rearranged lung cancers.

1.3 Managing Resected Lung Cancer as a Genomically Diverse Disease

This study attempts to change the paradigm of adjuvant therapy in NSCLC towards the delivery of personalized genotype-directed therapies. The power of broad genomic characterization has already been demonstrated in advanced disease, highlighted by the work of the Lung Cancer Mutation Consortium (5). This collaboration of academic cancer centers committed to performing genotyping of 10 different genes for 1000 lung cancer patients, accelerating accrual to biomarker-based clinical trials. This current trial, A151216 (ALCHEMIST), now lays the groundwork for applying the same paradigm to resected lung cancer. The ALCHEMIST trial will screen patients with resected NSCLC using widely accepted genomic assays (*EGFR* mutation testing and *ALK* FISH) in a centralized CLIA-certified laboratory using resources from NCI. There are several advantages to this approach. First, centralized assays will be used for *EGFR* and *ALK* genotype analyses, minimizing technical inconsistencies. Second, the access to molecular testing will not be constrained by physician preferences or insurance approval. Third, additional genomic tests can be added to this platform over time to study other genotype-defined subtypes of NSCLC. Fourth, this trial will present an opportunity to characterize the natural history of NSCLC carrying less common genotypes (other than *EGFR*-mutant and *ALK*-rearranged NSCLC) through coordination with research genomics performed at Center for Cancer Genomics (CCG). Finally, working closely with CCG, the ALCHEMIST trial will facilitate large scale unbiased comprehensive molecular (using genome, exome and transcriptome) analyses to identify additional potentially targetable gene alterations.

1.4 Adjuvant Immunotherapy for Patients without a Targeted Treatment Option

Nivolumab is an FDA-approved drug for the 2nd line treatment of squamous cell carcinoma of the lung (6). It has also demonstrated improvement in overall survival when compared to docetaxel in the 2nd line treatment of non-squamous non-small cell lung cancer (7). In non-squamous non-small cell lung cancer, it is evident that selection of patients with tumors that express PD-L1, as detected on tumor cells by immunohistochemistry, can enrich for response to nivolumab. The same enrichment for clinical benefit has been demonstrated in all non-small-cell lung cancers (not selected by histology) treated with the anti-PD-1 agent pembrolizumab (8). There is not an absolute correlation between tumor PD-L1 expression and response to

nivolumab, but the difference in response rate and survival between cohorts of PD-L1 positive and PD-L1 negative non-squamous non-small cell lung cancer patients is significant. In sites that have EA5142 IRB approved, PD-L1 status in resected tumors that are negative for EGFR and ALK will have prospective evaluation of PD-L1 in tumor samples, for the purposes of stratification and pre-specified subset analyses.

1.5 Facilitating the Development of Next-generation Genomics

Next-generation genomics is increasingly being adopted into research and clinical efforts around the country, such that the limitations of DNA sequencing are slowly being discovered. To move beyond DNA sequencing and study gene expression and epigenetics, a rigorous central effort is needed. Already, a third generation of genomic technologies is in development that allows RNA sequencing and methylomics on paraffin embedded specimens. In collaboration with CCG, this study will be an opportunity to develop these technologies on clinically-annotated specimens, and to eventually explore the clinical significance of the results of this genomic research. Additionally, this study will create a unique opportunity to study change in genomics over time, through the collection and analysis of diagnostic specimens collected at recurrence.

1.6 ALCHEMIST Study Design

The ALCHEMIST study will accrue patients that are potentially eligible for the adjuvant treatment studies (A081105 and E4512) and perform molecular testing using a central reference laboratory certified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Patients may either present prior to surgery with resectable NSCLC, or may present following complete resection (before or after adjuvant chemotherapy). All sites must submit patient's tissue for central *EGFR* and *ALK* genotyping. Patients will provide peripheral blood for matched normal DNA.

EA5142 IRB Approved sites: In addition to accruing the non-squamous patients, as described above, sites with EA5142 IRB approved will enroll squamous cell patients for PD-L1 testing. Additionally, those non-squamous patients who test (-) for ALK and EGFR will be tested for PD-L1.

1.7 Central Clinical Genotyping

Non-squamous patients: All patients (including those with local genotyping results) will have formalin-fixed tissue collected for central genotyping. The testing will be performed at Cancer Genetics, Inc. (formerly Response Genetics, Los Angeles, CA), a commercial CLIA-certified laboratory. ALK FISH will be performed using the Vysis break-apart probe and *EGFR* genotyping will be performed by sequencing of exons 18-21. EGFR/ALK genotyping results are expected to be provided to the treating clinician within 14 business days of submission so they can be used to determine eligibility for the randomized adjuvant studies, or to confirm the local results. Results will also be reported at intervals to the study team for upload into the Alliance database.

For sites with EA5142 IRB approved: Squamous patients and centrally (-) EGFR/ALK non-squamous patients tissue will be tested for PD-L1 at Cancer Genetics (formerly Response Genetics). The test results will be sent to the submitting site within 7 business days for squamous cell patients and within 21 business days for EGFR and ALK (-) patients. This group of patients will be assessed for participation in EA5142.

1.8 Advanced Genomics at CCG

In addition to the commercial genotyping at Cancer Genetics (formerly Response Genetics), tissue will be collected for research genomics by CCG. For those patients with a block available, this will be forwarded to the CCG after clinical testing at Cancer Genetics (formerly Response

Genetics). For those patients without a block available, 10 micron scrolls should be cut from a block and submitted (the thicker sections reduce oxidative tissue damage seen with standard thickness slides). A peripheral blood specimen will also be collected and sent to the CCG BCR to be used as a source of non-malignant ('germline') DNA. Specimens will be coded. Over the course of the study, the CCG will perform advanced genomic analysis of the resected lung cancer specimens in a research, non-CLIA environment. Following completion of the genomic analysis, the results can be matched with the clinical follow-up results using a link between the samples coded and the patient identifiers for correlative analyses. The results of these genomic studies will not be provided back to the patient or their treating physician.

1.9 Recurrence Biopsy

Subjects participating in the follow-up portion of the ALCHEMIST study, as well as those participating in the adjuvant therapeutic studies, may, at the discretion of the treating physician, undergo a standard-of-care diagnostic biopsy to confirm recurrence. If possible, core biopsies should be obtained as part of this recurrence biopsy. If available, paraffin embedded tissue from this biopsy should be sent to the NCI CCG BCR for additional research genomics (block preferred, scrolls with an H&E slide or unstained slides are acceptable). Please contact the BCR with any questions. In the event that re-biopsy tissue is not available, if clinical genomics testing is otherwise performed on the recurrence biopsy specimen, this data will be collected for research analysis as well.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To centrally test resected NSCLC for genetic mutations to facilitate accrual to randomized adjuvant studies.

2.1.2 To obtain clinically annotated tumor tissue and patient-matched non-malignant DNA from peripheral blood, as well as detailed epidemiologic and clinical follow-up data, to allow clinically annotated advanced genomic analyses in concert with the NCI Center for Cancer Genomics (CCG).

2.2 Secondary Objectives

2.2.1 To characterize the natural history of molecularly characterized NSCLC to allow subsequent development of targeted therapies against genotype-defined subpopulations in the adjuvant and recurrent settings.

2.2.2 To cross-validate local genotyping assays for *EGFR* and *ALK* with a central reference standard.

2.3 Exploratory/Other Objectives

2.3.1 To study the genomic evolution of lung cancers by comparing genomic characteristics at resection and at recurrence.

2.3.2 To understand reasons behind lack of enrollment to adjuvant targeted therapy studies for potentially eligible patients.

2.3.3 To study the clinical significance of circulating tumor DNA within the plasma cell-free DNA (cfDNA) from early stage lung cancer patients.

3.0 PATIENT PRE-REGISTRATION/REGISTRATION ELIGIBILITY CRITERIA

3.1 Patient Pre-registration Eligibility Criteria

For pre-surgical patients

- Suspected diagnosis of resectable non-small cell lung cancer. Cancers with a histology of "adenosquamous" are considered a type of adenocarcinoma and thus a "nonsquamous" histology. Patients with squamous cell carcinoma are eligible only if the registering site has EA5142 IRB approved.

  Cancers with a histology of "adenosquamous" are considered a type of adenocarcinoma and thus a "nonsquamous" histology.
- Suspected clinical stage of IIIA, II (IIA or IIB) or large IB (defined as size ≥4cm). Note: IB tumors <4cm are NOT eligible. Stage IB cancer based on pleural invasion is not eligible unless the tumor size is ≥4cm.

For post-surgical patients

- Completely resected non-small cell lung cancer with negative margins (R0). Patients with squamous cell carcinoma are eligible only if the registering site has EA5142 IRB approved.
- Pathologic stage IIIA, II (IIA or IIB) or large IB (defined as size ≥4 cm). Note: IB tumors <4cm are NOT eligible. Stage IB cancer based on pleural invasion is not eligible unless the tumor size is ≥4cm.

For all patients

- ECOG Performance Status 0-1
- Age ≥ 18 years
- No patients who have received neoadjuvant therapy (chemo- or radio-therapy) for this lung cancer
- No locally advanced or metastatic cancer requiring systemic therapy within 5 years prior to registration. No secondary primary lung cancer diagnosed concurrently or within 2 year prior to registration.
- No prior treatment with agents targeting EGFR mutation, ALK rearrangement, and PD-1/PD-L1/CTLA-4.
- No patients known to be pregnant or lactating
- Patients who have had local genotyping are eligible, regardless of the local result.
- No patients with recurrence of lung cancer after prior resection.

Note: Post-surgical patients should proceed to registration immediately following pre-registration.

3.2 Patient Registration Eligibility Criteria

- Completely resected NSCLC with negative margins (R0). Cancers with a histology of "adenosquamous" are considered a type of adenocarcinoma and thus a "nonsquamous" histology. Patients with squamous cell carcinoma are eligible only if the registering site has EA5142 IRB approved.
- Pathologic stage IIIA, IIA or IIB, or large IB (defined as size ≥ 4cm). Note: IB tumors <4cm are NOT eligible. Stage IB cancer based on pleural invasion is not eligible unless the tumor size is ≥4cm.
- Tissue available for the required analyses (either clinical tissue block or slides and scrolls, see Section 5.1)

- In order to allow for time for central genotyping and eligibility for the ALCHEMIST treatment trial, patients must register within the following eligibility windows, depending on the adjuvant treatment approach:
  1. If no adjuvant therapy, register patient within 75 days following surgery.
  2. If adjuvant chemotherapy **or** radiotherapy only, register patient within 225 days following surgery.
  3. If adjuvant chemotherapy **and** radiation, register patient within 285 days following surgery.

4.0 PATIENT PRE-REGISTRATION AND REGISTRATION

Sites must have A151216 and the two treatment trials A081105 and E4512 IRB approved before registering patients to A151216.

All patients will pre-register to A151216. **Those patients that have already had surgery will complete the registration process at the same time as pre-registration**. Pre-op patients will be pre-registered and will then be registered following surgery, as long as all the registration eligibility criteria have been met. Patients may be receiving adjuvant therapy at the time of registration to A151216.

4.1 Pre-registration Requirement

Informed Consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and consent form is required.

4.2 Patient Registration/Randomization

4.2.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed Statement of Investigator Form (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed Financial Disclosure Form (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the CTEP Investigator Registration Help Desk by email at <pmbregpend@ctep.nci.nih.gov>.

4.2.2 CTEP Associate Registration Procedures/CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the CTEP Associate Registration Help Desk by email at <ctepreghelp@ctep.nci.nih.gov>.

4.2.3 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the A151216 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the *Alliance* link to expand, then select trial protocol A151216
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for A151216 Site Registration:

- IRB approval (for sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) Regulatory Tab Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.2.4 Patient Enrollment through OPEN

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3 Study-specific Patient Registration Procedures

All patients will be pre-registered and registered to A151216 prior to submission of tissue for molecular testing. Patients can be pre-registered to A151216 pre-operatively or post-operatively.

Pre-operative patients:

Pre-operative patients will be pre-registered to A151216 prior to surgery. Following surgery and confirmation of registration eligibility criteria, patients will be registered to A151216 using the Alliance patient ID number assigned at pre-registration. This number will be entered into the OPEN registration system. You will then receive a confirmation of registration for your records.

Post-operative patients:

Post-op patients will pre-register and register to A151216 at the same time. Following confirmation of registration eligibility criteria, the CRA will register the patient by entering the Alliance patient ID number assigned at pre-registration into the OPEN registration system. The OPEN system will provide the institution with a printable confirmation of registration. Please print this confirmation for your records.

Registration Steps for Patients with Local Results:

Patients with a local *EGFR* mut+ or *ALK*+ test will pre-register and register to A151216 and may proceed to be screened for the appropriate treatment trial. All tissue and blood is still required for the genotyping and genomic research. These patients do not need to wait the 14 days for confirmation of the positive test to enter the treatment trial. If the central laboratory (Central Genetics) does not confirm the local positive test, patients may still be registered to the appropriate adjuvant treatment trial.

Patients with a local *EGFR* mut negative and *ALK* negative test will register to A151216 and will still have all the required tissue and blood submitted for genotyping and genomic analysis. Once the results from the central genotyping have been received patients will be considered for one of the treatment trials if they are (+) for either EGFR or ALK. If a patient is found to be (-) locally for both EGFR and ALK but are (+) from the central testing they may be entered onto one of the treatment trials.

Sites with EA5142 IRB approved:

Squamous patients registered to A151216 will be tested for PD-L1 only (they will not have EGFR/ALK testing). Additionally, non-squamous patients testing (-) for EGFR and ALK will also undergo PD-L1 testing. For the squamous cell patients PD-L1 test results will be sent to the submitting site from Response Genetics within 7 business days. Non-squamous cell patients having a (-) EGFR and ALK test result will receive PD-L1 test results within 21 business days of submission. These patients will be assessed for enrollment on EA5142.

Epidemiological questionnaire for all patients: Following registration, a CRA will complete an epidemiological questionnaire to be used for comprehensive clinical annotation of the planned research genomics at CCG.

5.0 SPECIMEN COLLECTION AND SUBMISSION

5.1 Specimen Submission Overview and Timeline

Kits are available for the submission of whole blood to the BCR. Kits are not available for specimen submission to Cancer Genetics and the recurrence biopsy to BCR. **Kits for whole blood submission should be ordered using BioMS. Once sites have Update #3 IRB approved kits for collecting the blood can be ordered using BioMS.** At site IRB approval of Update #3 each site should order 3 kits for collection. Kits should then be re-ordered once they have been used. Please note: Kits are available for whole blood collection only, not for tissue submission to Cancer Genetics or recurrence biopsy submission to the BCR.

Specimen	Timepoint	Ship to	Kit available?
1) Whole Blood	Obtain following surgery, up to 30 days following registration (30 days is preferred, but collection at a later time is acceptable), submit within 1 week of collection	BCR	Yes
2) Tissue Block	Submit following registration to A151216	Cancer Genetics (formerly Response Genetics)	No
OR			
Slides AND Scrolls (w/ one H&E slide)	Submit following registration to A151216	Slides to Cancer Genetics (formerly Response Genetics) Scrolls and H&E slide to BCR	No
3) Recurrence Biopsy (if done)	Submit at progression	BCR	No
A diagram of the submission process is included in Appendix I.			

1) Blood: All patients will have three whole blood specimens obtained at any point after surgery up to 30 days following registration. Blood should be shipped to the BCR within 1 week of collection. It is preferred that blood be collected during the period between surgical resection and initiation of any adjuvant therapy. Later blood collection, including outside of the 30-day window following registration, is discouraged but will be accepted.

2) Tumor blocks or cut slides and tissue scrolls: Following registration, blocks or slides will be submitted to Cancer Genetics (formerly Response Genetics) laboratory for EGFR and ALK testing. If slides are submitted to Cancer Genetics then sites must submit tissue scrolls and an H&E slide to the BCR. (Tissue scrolls are "shavings" from the pathology block.)

3) Recurrence Biopsy: If a biopsy is done at recurrence tissue will be submitted to the BCR.

5.2 Blood Collection and Submission for All Patients

Blood should be obtained at any point after surgery up until 30 days following registration. It is preferred that blood be collected during the period between surgical resection and initiation of any adjuvant therapy. Later blood collection, including outside of the 30-day window following registration, is discouraged but will be accepted. Three whole blood specimens will be collected: one 10ml EDTA tube (provided in the kit) and two 10ml 10cc cell-free DNA blood collection tubes (BCT) from Streck (provided in the kit). **Please store all blood at room temperature prior to shipping.**

Ship at room temperature with the ambient packs included in the kits provided. Airbills may be requested for shipments to the NCI CCG by contacting Kristen Leraas at: Kristen.Leraas@nationwidechildrens.org. **Please do not refrigerate or freeze the blood samples nor use dry ice for shipment**. Blood specimens are to be submitted Monday through Thursday (NO Saturday delivery) to:

NCI CCG Biospecimen Core Resource
Nationwide Children's Hospital
Attn: Kristen Leraas
700 Children's Dr., WA1340
Columbus, OH 43205
Tel: 614-355-3589

5.3 Tissue Preparation

See Appendix II for further information regarding block and slide submission to Cancer Genetics (formerly Response Genetics).

Study Tissue Block: At the time of surgical resection and gross pathology review, an additional segment of grossly apparent primary tumor tissue will be embedded for study purposes only. This tumor tissue block will not be returned to the site. Prior to distribution of the block, the site should cut, stain, and review one section of the study block to confirm that it is representative of the clinical diagnosis document tumor cellularity by histological review. Cancer Genetics (formerly Response Genetics) will then forward the remaining block to the BCR for genomic research.

OR

Clinical Tissue Block: The site pathologist should identify one block of primary tumor tissue from the case that is representative of the histological diagnosis, contains at least 1 cm^2 of tissue on the block face, and document tumor cellularity by histological review. Cancer Genetics (formerly Response Genetics) will then forward the block to the BCR for genomic research. Note that if the block is required by the site at some future date for clinical patient management, the block will be returned to the site within upon a written request, if physically possible, but this cannot be guaranteed.

OR

Tissue Slides and Tissue Scrolls

Tissue Slides: The site pathologist should identify one block of primary tumor tissue from the case that is representative of the histological diagnosis and document tumor cellularity by histological review. A total of five (5) 10-micron sections plus eight (8) 5-micron sections should be cut and mounted on positively-charged glass slides and shipped to Cancer Genetics (formerly Response Genetics).

Tissue Scrolls (see scroll calculator on the Alliance or CTSU website to calculate amount of scrolls needed): The site pathologist should also identify one block of primary tumor tissue from the case that is representative of the histological diagnosis and document tumor cellularity by histological review (preferably, this will be the same block from which slides were cut for shipment to Cancer Genetics). One 5-6 micron section slide should be cut and stained with H/E, followed by a number of 10 micron tissue sections (scrolls, also known as "shavings") calculated as follows:

Number of tissue sections = 12 / (0.01 * *L* * *W*);

where L, W are the approximate cross-sectional length and width of the tissue surface, in mm.

Site pathologists may use the scroll calculator on the A151216 webpage to quickly determine the number of sections needed based upon tissue cross sectional area.

Scrolls should be sealed inside a microcentrifuge tube and a final 5-6 micron section should be cut and stained with H/E. The scroll and slide should be labeled with the A151216 patient ID and the protocol ID (A151216) prior to shipping. **The sealed tube of tissue scrolls and both H/E stained referenced slides should be shipped to the BCR on the same day of sectioning. Please contact the BCR for a priority overnight FedEx airbill.** To ensure rapid processing, note that blocks should not be sectioned or shipped on a Friday-Saturday, or a day before a holiday.

5.4 Specimen Submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM. **Additionally, sites will use BioMS to request kits for the blood draw.**

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A151216) and Alliance patient number.

The de-identified pathology report, being submitted with the sample to Cancer Genetics, should include the protocol number (A151216), patient number and patient's initials.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Thursday by overnight service to assure receipt is required. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

5.4.1 Tissue Block or Slide Submission

At the time of biospecimen submission, a blank Clinical Assay Request form will be automatically printed at the same time as the standard BioMS shipping manifest. This form should be completed by appropriate clinical personnel and included with the biospecimen shipment to Cancer Genetics (formerly Response Genetics). It is needed, independent of the BioMS shipping form, for returning EGFR and ALK testing results to the clinical site. Please also send a copy of the patient's pathology report to Cancer Genetics (formerly Response Genetics). This pathology report will NOT be forwarded to the BCR.

All tissue specimens for ALK/EGFR and/or PD-L1 analysis should be sent to Cancer Genetics:

Cancer Genetics
Attn: Director of Pharmaceutical Services
1640 Marengo Street
Suite 410
Los Angeles, CA 90033
Tel: 323-224-3900 x210

Once Cancer Genetics has analyzed tissue from the tissue block they will forward it to the NCI BCR for genomics. Sites submitting slides to Cancer Genetics will also need to submit scrolls and an H&E slide to the NCI BCR for genomics.

5.4.2 Scrolls and H&E Slides Submission:

All scrolls and H&E slides (for those sites submitting slides to Cancer Genetics and scrolls to BCR) are to be submitted Monday through Thursday (NO Saturday delivery), to:

NCI CCG Biospecimen Core Resource
Nationwide Children's Hospital
Attn: Kristen Leraas
700 Children's Dr., WA1340
Columbus, OH 43205
Tel: 614-355-3589

The BCR will bank tissue for future studies.

5.5 Tissue Submission at Progression

Patients undergoing a diagnostic biopsy at recurrence will have tissue submitted to the BCR, if available. Sites should submit FFPE material at room temperature (block preferred, scrolls with an H&E slide or unstained slides are acceptable) to the address below. The material should be labeled with the A151216 patient ID and the protocol ID (A151216). Please contact the BCR for questions on how to process FFPE scrolls or unstained slides.

If there were clinical genomics done on a recurrence specimen for any patient, regardless of whether or not there is recurrence tissue available for submission, sites should submit the molecular report on the recurrence specimen in RAVE.

Recurrence biopsies are to be submitted Monday through Thursday (NO Saturday delivery), to:

NCI CCG Biospecimen Core Resource
Nationwide Children's Hospital
Attn: Kristen Leraas
700 Children's Dr., WA1340
Columbus, OH 43205
Tel: 614-355-3589

The BCR will bank the tissue for future studies.

5.6 Specimen Analysis

5.6.1 EGFR and ALK Genotyping

All patients (including those with local genotyping results) will have formalin-fixed tissue collected for central genotyping. The testing will be performed at Cancer Genetics (formerly Response Genetics, Los Angeles, CA), a commercial CLIA-certified laboratory. ALK FISH will be performed using the Vysis break-apart probe and EGFR genotyping will be performed by sequencing of exons 18-21. Genotyping results are expected to be provided to the treating clinician within 14 business days of submission so they can be used to determine eligibility for the randomized adjuvant studies, or to confirm the local results. Results will also be reported at intervals to the study team for upload into the Alliance database.

5.6.2 Next Generation Sequencing

In addition to the commercial genotyping at Cancer Genetics (formerly Response Genetics), tissue will be collected for research genomics by CCG. For those patients with a block available, this will be forwarded to the CCG after clinical testing at Cancer Genetics (formerly Response Genetics). For those patients without a block available, 10 micron scrolls should be cut from a block and submitted (the thicker sections reduce oxidative tissue

damage seen with standard thickness slides; please see the scroll calculator on the Alliance and CTSU website for the number of scrolls to be cut). A peripheral blood specimen will also be collected and sent to the CCG BCR to be used as a source of non-malignant ('germline') DNA. Specimens will be coded. Over the course of the study, the CCG will perform advanced genomic analysis of the resected lung cancer specimens in a research, non-CLIA environment. Following completion of the genomic analysis, the results can be matched with the clinical follow-up results using a link between the samples coded and the patient identifiers for correlative analyses. The results of these genomic studies will not be provided back to the patient or their treating physician.

All remaining tissue will be stored at the CCG BCR for future studies.

5.6.3 PD-L1 IHC

To assess the role of PD-L1 protein expression as a biomarker, tumor tissue will be collected prospectively from all squamous cell patients in this study. PD-L1 expression is defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using the validated DAKO PD-L1 IHC assay. PD-L1 positive is defined as >= 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells and PD-L1 negative is defined as < 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells. PD-L1 unevaluable is defined for subjects with no quantifiable PD-L1 expression at baseline either due to tumor biopsy specimens not available, or tumor tissue samples not optimally collected or prepared, or the hampered staining.

5.6.4 Genomic Analysis of Cell-free Plasma DNA

Two blood specimens will be collected for analysis of plasma cfDNA. Blood will be spun into plasma following receipt at the BCR. Plasma will be frozen until time of analysis, at which time DNA will be extracted from one specimen for genomic analysis; the second plasma specimen will be saved for future confirmatory studies. Over the course of the study, the CCG will coordinate advanced genomic analysis of the resected lung cancer specimens in a research, non-CLIA environment. Following completion of the genomic analysis, the results can be matched with the clinical follow-up results using a link between the samples coded and the patient identifiers for correlative analyses. The results of these genomic studies will not be provided back to the patient or their treating physician. A third blood specimen, collected in EDTA, will be used as a germline control for the planned tumor genomics.

5.7 Test Results from Cancer Genetics (formerly Response Genetics)

PD-L1 results for squamous patients will be sent to the sites within 7 business days of receipt.

EGFR/ALK results for non-squamous patients will be sent to sites within 14 business days by FAX. If the EGFR and ALK are both (-) the specimen will then be tested in PD-L1 for those sites who have EA5142 IRB approved. The PD-L1 test results will then be sent to the submitting sites within 21 business days of receipt. **Note: Only patients who are ALK and EGFR (-) will have the PD-L1 testing done.**

Once Cancer Genetics (formerly Response Genetics) has completed testing on tissue blocks they will send the remaining block to the BCR for genomic analyses and storage.

5.8 Inadequate Submissions

5.8.1 Cancer Genetics (formerly Response Genetics)

If the blocks or slides submitted to Cancer Genetics (formerly Response Genetics) for molecular testing are inadequate, or fail to yield a result, Cancer Genetics will contact the site requesting an additional submission.

5.8.2 Biospecimen Core Resource

If the remaining tissue from Cancer Genetics or the scrolls submitted by sites are found to be inadequate for genomic analysis (DNA or RNA yield) the BCR will contact the site. If a site would like to submit additional specimens to BCR for genomic studies, please contact the BCR at 614-355-3589.

6.0 CLINICAL DATA REQUIREMENTS

6.1 Follow-up

- All patients NOT going on A081105, E4512, or EA5142 will be followed on A151216 (every 6 months for 5 years). If a clinic visit did not occur within the 6 month window a site may call to follow the patient.

Patients that meet one or more of the following criteria will not be followed on A151216:

- Patients that are pre-registered only. This will be a very small percentage of patients who are registered pre-operatively and are found at surgery not to be eligible to participate on A151216.
- Patients enrolled on a treatment trial will be followed on the respective trial.

6.2 Data Collection and Submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

7.0 STATISTICAL CONSIDERATIONS

This is a central biomarker screening trial that is designed to screen resected lung cancers for targetable genomic alterations.

7.1 Sample Size

It is estimated that up to 8000 patients may need to be genotyped in order to fully accrue to the *EGFR* (estimated prevalence in advanced disease setting is 15%) and *ALK* (estimated prevalence in advanced disease setting is 5%) studies. We anticipate approximately 10% of patients screened in the adjuvant setting to have either the EGFR mutation or the ALK rearrangement. Fewer patients may need to be screened depending upon adoption of pre-screening strategies such as clinical selection or local genotyping.

It is estimated that up to 1000 patients with (-) EGFR and ALK non-squamous NSCLC and an additional 300 squamous cell NSCLC patients will be tested for PD-L1 to complete enrollment on EA5142. This assumes 20-25% of patients enrolled to EA5142 will have squamous cell carcinoma.

Thus, up to 8300 patients will be accrued to this screening trial to facilitate accrual to the three adjuvant trials: A081105, E4512 or EA5142.

7.2 Baseline Clinical Information

At time of registration, patients will assist the CRA in completing the on-study forms, to report characteristics that may be associated with the planned genomic analysis, including the following data:

- Age, gender, racial background
- Personal history of cancer and other pulmonary disorders
- Family cancer history (including family smoking history)
- History of occupational and environmental exposures including prior radiation
- Smoking history, including second hand smoke exposure

7.3 Clinical Follow-up Plan

Given the large number of subjects being followed, clinical follow-up will be kept to a minimum. All patients will be followed until otherwise notified by the Statistical Center. Patients will be contacted every 6 months to assess the following datapoints:

- Adjuvant therapy received (Y/N, which agents)
- Recurrent (Y/N)
- Date of recurrence
- Site of recurrence
- Pathologic confirmation of recurrence (Y/N, type of biopsy)
- Smoking Status
- Dead (Y/N)
- Date of death

In the instances where BCR has determined that there is not usable tissue for genomic analysis, the Data Center will contact the site to let them know patient follow-up may be discontinued. Sites should not discontinue patient follow-up before the 5-year point unless instructed to do so by the Data Center.

7.4 Endpoints

7.4.1 Primary Endpoint

There are two primary endpoints to this trial:

- Central clinical genotyping to facilitate accrual to the adjuvant Intergroup studies as measured by rate of accrual.
- Feasibility of research grade FFPE tissue collection for CCG analysis, as measured by adequate specimens collected per month. The goal is to achieve a collection rate over 100 adequate cases per month, to allow collection of at least adequate 4800 specimens over a four-year period. Importantly, this collection rate will depend upon specimen adequacy reports provided by the CCG.

7.4.2 Secondary Endpoints

There are two secondary endpoints for this trial:

- **2-year disease free survival (DFS) rate for lung cancers which are wild-type for EGFR and ALK.** Using genomics performed at CCG, DFS rate will be calculated for each genotype-defined population constituting greater than 1% of the study cohort. DFS is defined as the time from resection to the earliest of documented disease recurrence confirmed by biopsy, development of a new lung cancer confirmed by biopsy, or death from any cause. We estimate at least 80 patients in each of these rare genotype-defined subsets, which will allow estimation of the 2 year DFS rate within 11.2% points with 90% confidence. This will serve as a historical control for future single-arm phase II trials of targeted adjuvant agents in these populations. Note: Patients enrolled in adjuvant targeted therapy trials, such as the adjuvant nivolumab trial (EA5142), will be excluded from this estimate of DFS.
- **Agreement of local genotyping methods (direct sequencing of EGFR, ALK FISH) with central CLIA genotyping.** 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. The 95% confidence intervals for 90% success rates such that the lower limit is at least 80% or higher are given in the following table for different sample sizes:

Sample Size	Number of successes	95% Confidence Interval (lower, upper)
100	90	82.4, 95.1
150	135	84.0, 94.3
200	180	85.0, 93.8
250	225	85.6, 93.4

7.4.3 Exploratory/Other Endpoints

- **Spectrum of new mutations identified at recurrence.** Genomic analysis will be performed on tissue collected at time of recurrence and compared to baseline genomics. New mutations in key oncogenes and tumor suppressor genes (PIK3CA, PTEN, etc) will be quantified. It is hypothesized that a greater number of new alterations will be identified in patients whom received adjuvant chemotherapy as opposed to those not receiving adjuvant chemotherapy.

- The reasons behind why potentially eligible ALK-rearranged/EGFR mutant patients decline to enroll onto the adjuvant trials will be summarized. Specifically, the proportions of patients who decline to enroll because of concern with randomization, or not needing further therapy versus those who become otherwise ineligible due to recurrent disease or missing the enrollment window will be catalogued. Such summaries will be periodically reviewed by the study team to understand if any changes or clarifications are needed to the protocol or if additional educational material needed for the sites to help facilitate accrual to the adjuvant studies.
- Simple exploratory analyses will be used to better understand the variability in the levels of baseline cfDNA based on the timing of collection of these samples. The levels of cfDNA (stratified by the timing of collection) will be correlated with clinical outcomes of overall survival and disease-free survival using Kaplan-Meier approach as well as exploratory Cox proportional Hazards models adjusted for baseline smoking, patient, and tumor characteristics as well as treatment information.

7.5 Sample Size

The sample size will depend partially upon the prevalence of EGFR mutations and ALK rearrangements, and partially upon the degree of selection used when investigators are accruing patients. With no clinical selection, up to 8300 patients will need to be screened to fully accrue the randomized adjuvant studies. This is because ALK rearrangements are present in 4-5% of lung adenocarcinoma, such that 8000 patients must be screened to identify the 366 subjects for the crizotinib study. However, if investigators decide to use clinical selection methods to determine which patients to screen, and primarily accrue never-smokers, then half as many patients must be screened (EGFR mutations and ALK rearrangements are twice as prevalent in never-smokers as in the general adenocarcinoma population). Alternatively, some centers may genotype resected cancers locally and then accrue patients with a known EGFR mutation or ALK rearrangement – this would further decrease the total number of patients needed to be centrally genotyped to achieve the study aims.

An additional cohort of 300 patients with resected squamous cell carcinoma will be enrolled for the purposes of PD-L1 screening and for assessment to be enrolled on EA5142.

7.6 Analysis Plan

Accrual rate to the adjuvant studies will be monitored every 3 months, and discussed between the study teams coordinating the ALCHEMIST study and the adjuvant studies. If accrual is inadequate, then the ALCHEMIST study will initiate strategies to improve accrual, including opening the screening study at new centers and developing strategies for genotyping at participating centers to improve catchment. Specimen collection rate will also be monitored every 3 months and discussed between the ALCHEMIST study team and the CCG. If collection of adequate specimens is insufficient, then the ALCHEMIST study will initiate strategies to improve specimen adequacy.

7.7 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	129	166	295
Not Hispanic or Latino	4482	3523	8005

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Ethnic Category: Total of all subjects*	4611	3689	8300
Racial Category			
American Indian or Alaskan Native	19	19	38
Asian	0	0	0
Black or African American	239	185	424
Native Hawaiian or other Pacific Islander	0	0	0
White	4352	3486	7838
Racial Category: Total of all subjects	4610	3690	8300

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

8.0 ETHICAL AND PRIVACY CONSIDERATIONS

8.1 Restricted Access to Genomic Data

The research genomic studies will generate genetic data unique to an individual ("genetic fingerprints", or genotypes). These data are not directly tied to an identified individual, and the clinical information associated with these data will be de-identified. Nevertheless, a risk exists that the genetic data could lead to the re-identification of a participant or relative. Consequently, NIH policy is that individual genetic data from the characterization studies are kept in a restricted-access tier of the database.

To be authorized to access the restricted tier of data, Investigators must submit an application to a Data Access Committee (DAC) of the National Institutes of Health designated to review applications for the Alchemist initiative. Upon approval by the DAC that the access request is for bona fide research purposes, the Investigator, scientists under their control, and their institution must subscribe to a Data Use Certification (DUC) that controls their ability to access the data, redistribute the data, prohibits the re-identification of participants, and includes requirements for data security. Controlled-access data are for General Research Use, i.e. usable

for any genetic studies; there are no data use restrictions with respect tofield of study and users may apply data to any legitimate research including non-cancer research-related discovery.

9.0 REFERENCES

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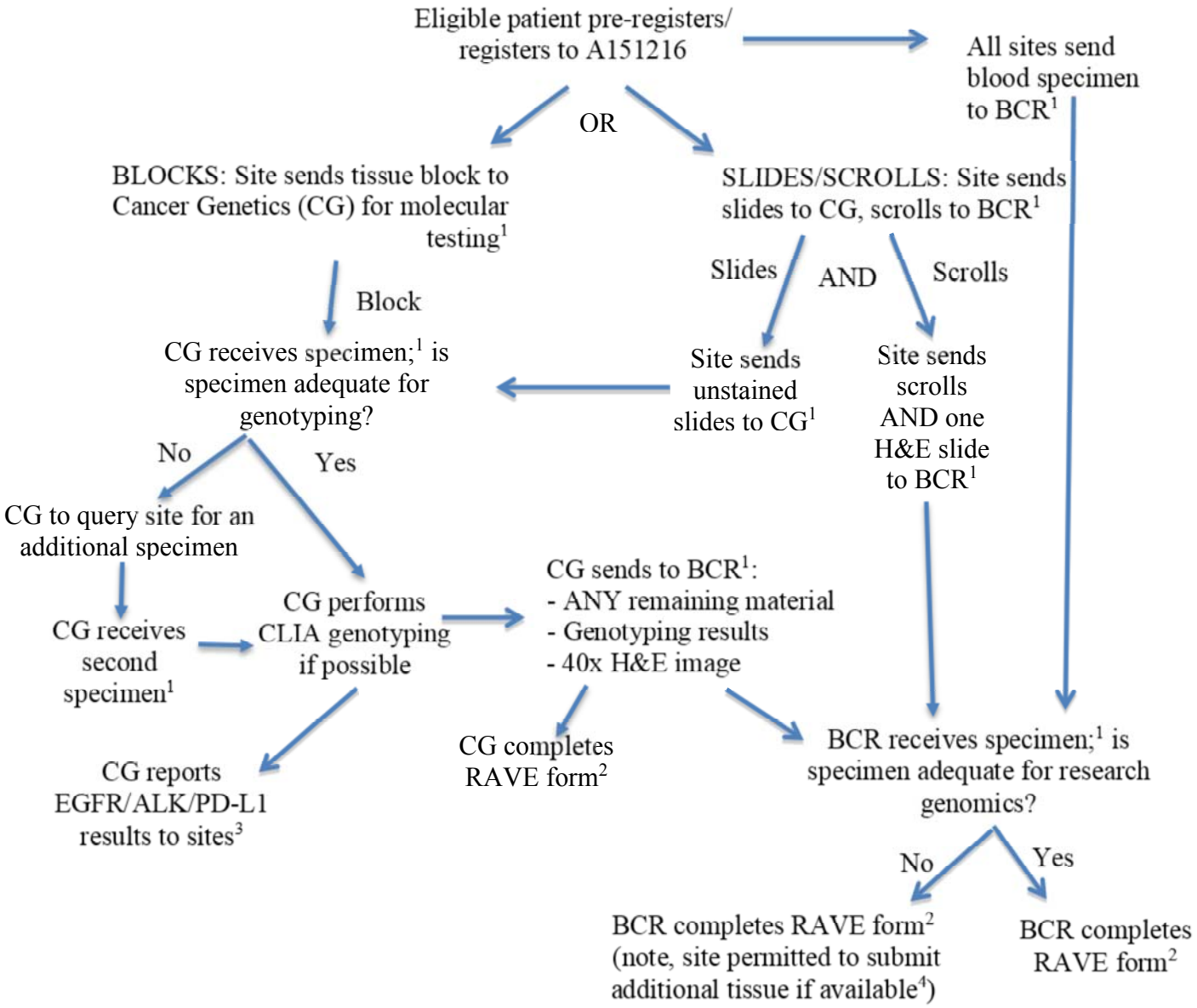
APPENDIX I

For laboratory use: ALCHEMIST laboratory flow diagram



[1]All specimens sent or received must be logged into BioMs.
[2]Sites will have view access to these results & adequacy CRFs. Alliance Data Center will review specimen adequacy results at least quarterly to identify problems and implement improvements.
[3]EGFR/ALK and PD-L1 results will be returned by FAX to the CRA and ordering clinician using contact information from requisition. The EGFR/ALK results are sent within 14 business days of receipt. In squamous patients PD-L1 testing will be returned within 7 business days of receipt; PD-L1 results will be returned within 21 business days in the EGFR/ALK (-) patients.
[4]Sites with inadequate specimens will be contacted by the BCR to discuss resubmission.

APPENDIX II

Laboratory Manual for ALK/EGFR Testing Tissue Submission ALCHEMIST

CANCER GENETICS (FORMERLY RESPONSE GENETICS) CONTACT INFORMATION:

Miriana Moran, PhD, PMP
Director of Pharmaceutical Services
miriana.moran@cgix.com
Office: 213-863-0190

Sharlyn Silang
Project Manager, Pharmaceutical Services
sharlyn.silang@cgix.com
Office: 323-224-3900

Shipping Address:
Cancer Genetics
Pharmaceutical Services
1640 Marengo Street
Suite 410
Los Angeles, CA 90033

BLOCK AND SLIDE PREPARATION

PREPARATION OF PARAFFIN EMBEDDED TISSUE BLOCKS

Tissue blocks are preferred. Blocks should be submitted as soon as possible after consent is obtained.

- Standard dimensions of block – approximately 4cm x3cm
- If multiple blocks available, **submit block with most tissue**; do **not** send multiple blocks per subject.
- The subject identifier and block number must be written on the block in pencil and be clearly legible.
- Wrap blocks in a foam pouch and place into slide container.
- See packaging instructions.

PREPARATION OF TISSUE SLIDES

If the tissue block is unavailable, prepare tissue slides.

- **The number of slides to be submitted is** five (5) 10-micron sections plus eight (8) 5-micron sections.
- **Positively charged frosted ended slides must be used.**
- Section a single section containing tissue onto each slide.
- Sections **must** be from the same tissue block.
- Subject identifier, and block number must be written legibly in pencil on the frosted end of the slide.
- Slides must **not** be baked or melted.
- Cover slips must **not** be used.
- Sections must **not** be stained.
- Place slides in slide box.
- See packaging instructions.

IMPORTANT HIGHLIGHTS ABOUT TISSUE SAMPLE PREPARATION

- Tissue blocks are preferred.
- Multiple blocks per visit should not be submitted.
- Tissue sections **must** come from the same block.
- The entire clinical assay request form must be completed and include the biopsy collection date and the biopsy collection site. Identifiers including subject identifier, and block ID number must be entered on the requisition form and must match the identifiers on the tissue blocks or slides.
- Only the required number of slides or a block of tissue should be submitted.

AVOID THE FOLLOWING

- Submission of the incorrect number of slides
- Submission of stained slides
- Incorrect sample packaging
- Incorrect and/or incomplete clinical assay request form (e.g. Subject identifier and block number missing from the block or slides)

OVERVIEW OF TUMOR BLOCK SHIPPING

1. Fill out the Clinical Assay Request Form and place in the foam mailer. 	2. Ensure the tissue block is labeled legibly with the Subject Identifier and block number, written in pencil. 	3. Place the tissue block in a slide box. 
4. Place the slide box in the foam mailer. 	5. Ship ambient to Cancer Genetics (formerly Response Genetics) Shipping Address: Cancer Genetics Pharmaceutical Services 1640 Marengo Street Suite 410 Los Angeles, CA 90033	

OVERVIEW OF SLIDE SHIPPING

1. Five (5) newly cut serial tissue sections cut at 10-micron plus eight (8) cut at 5-micron are mounted on positively charged frosted ended slides. 	2. Ensure that subject identifier and block number are written legibly in pencil on the frosted end of each slide. 	3. Place the slides in a slide box. 
4. Place the slide box and the Clinical Assay Request Form in a foam mailer. 	5. Ship ambient to Cancer Genetics (formerly Response Genetics) Shipping Address: Cancer Genetics Pharmaceutical Services 1640 Marengo Street, Suite 410 Los Angeles, CA 90033	