**Alliance Study A151216 – Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST)**

Committee: Respiratory
Study Chair: Geoffrey Oxnard, MD

Study Statisticians: Sumithra Mandrekar, Ph.D.
Shauna Hillman, M.S.

1.0 OBJECTIVES

Primary

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

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).

Secondary

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.

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

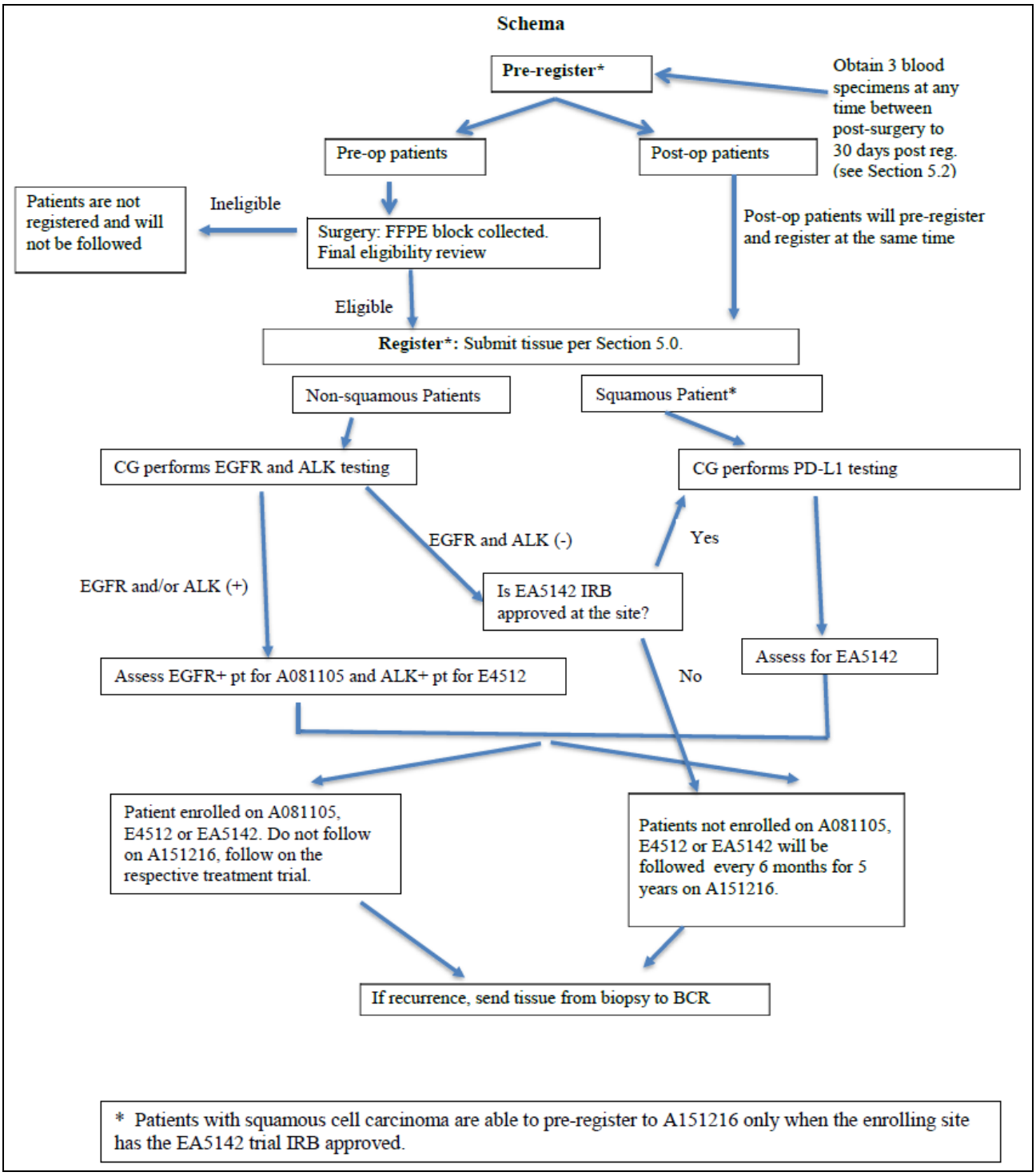
Exploratory/Other

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

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

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

## 2.0 CURRENT SCHEMA




## 3.0 ELIGIBILITY CRITERIA

Pre-registration:

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.
- 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 ≥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 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.

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

Registration:

- 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 protocol 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:
    - If no adjuvant therapy, register patient within 75 days following surgery.
    - If adjuvant chemotherapy or radiotherapy only, register patient within 225 days following surgery.
    - If adjuvant chemotherapy and radiation, register patient within 285 days following surgery.

## 4.0 TREATMENT SCHEDULE

Not Applicable

## 5.0 STUDY DESIGN

5.1 Study Phase/Type of Design/Stratification Factors

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

5.2 Primary Endpoint

There are two primary endpoints to this trial: 1) Central clinical genotyping to facilitate accrual to the adjuvant Intergroup studies as measured by rate of accrual. 2) Feasibility of research grade FFPE tissue collection for Center for Cancer Genomics (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 4800 adequate specimens over a four-year period. This collection rate will depend upon specimen adequacy reports provided by the CCG.

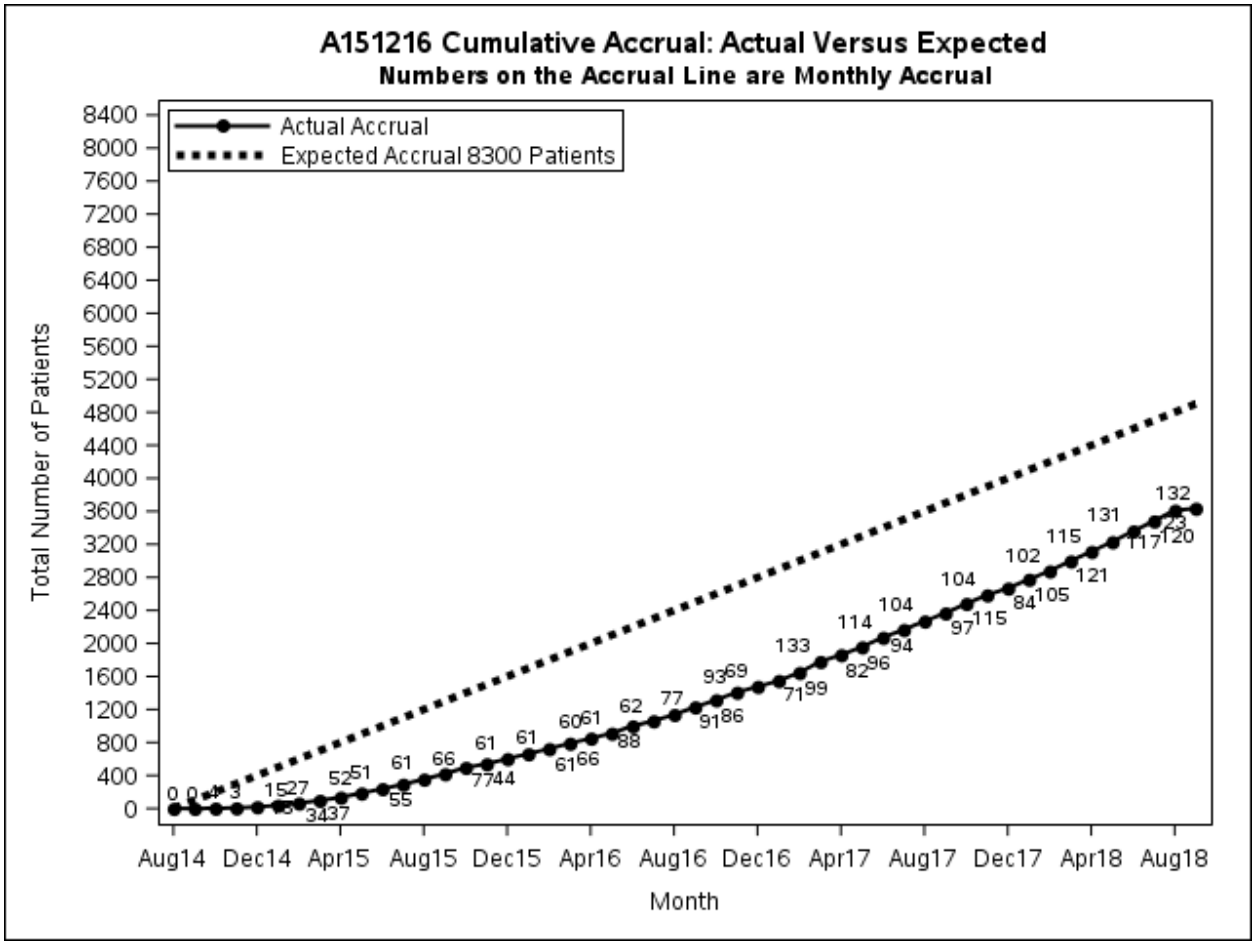
5.3 Target Accrual

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 to the randomized adjuvant studies. 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.

The target accrual for this study is 8300 patients. The target accrual rate is 100 patients per month.

## 6.0 CURRENT ACCRUAL

| | |
|---|---|
| Study Activation Date | 08/18/2014 |
| Target Accrual (n) | 8300 |
| Patients screened or pre-registered (n) | 3676 |
| Current Accrual (n) | 3636 |
| Expected Accrual Rate | 100/month |
| Accrual Rate – Since activation | 74/month |
| Accrual Rate – Past 12 months | 112/month |
| Accrual Rate – Past 6 months | 120/month |
| Projected closure date for a trial open for more than one year (based on accrual rate from past 12 months) | 02/23/2022 |




7.0 CURRENT STUDY STATUS

This study opened on 8/18/2014, has pre-registered 3676 patients and registered 3636 patients.

Per the protocol update #01, study schema has been reorganized to match the Section 3.0 of the protocol. There are now pre-registration eligibility criteria for pre-surgical patients, post-surgical patients, and for all patients. All patients with local genotyping are eligible, regardless of the local result. The entire section of 3.1 the pre-registration eligibility criteria has been reorganized for better understanding.

Per the protocol update #02, all sections of the protocol were revised to include the requirements for the addition of new EA5142 trial, adjuvant nivolumab in resected lung cancers (ANVIL) to A151216 screening trial. Sites with EA5142 IRB approval are allowed to accrue squamous patients for PD-L1 testing. In those sites with EA5142 IRB approval, non-squamous patients without EGFR and ALK mutations eligible for A081105 and E4512 will be PD-L1 tested.

Per the protocol update #03, the study schema, study objective, and the sections of specimen collection and submission; and statistical considerations were revised to include the new genomic analysis correlative study to study the clinical significance of circulating tumor DNA within the plasma cell-free DNA (cfDNA) from early stage lung cancer patients. The study schema, pre-registration/registration eligibility criteria were also revised for better understanding.

Per the protocol update #04, minor editorial have been made to the protocol section of specimen collection and submission. The model consent was updated to remove the reference to the placebo

in regards to E4512 and A081105 trials, on which patients will be randomized to drug vs observation instead of drug vs placebo.

Abstract entitled: “Adjuvant targeted therapy following standard adjuvant therapy for resected NSCLC: An initial report from ALCHEMIST (Alliance A151216)” was accepted as a poster presentation for IASLC WCLC 2018.

Manuscript references:
Gerber DE, Oxnard GR, Govindan R. ALCHEMIST: Bringing genomic discovery and targeted therapies to early-stage lung cancer. Clin Pharmacol Ther. 2015 May; 97(5): 447-450. doi:10.1002/cpt.91.

Alden RS, Mandrekar SJ, Oxnard GR. Designing a definitive trial for adjuvant targeted therapy in genotype defined lung cancer: the ALCHEMIST trials. Chin Clin Oncol. 2015 Sep; 4 (3): 37.

Govindan R, Mandrekar SJ, Gerber DE, Oxnard GR, Dahlberg SE, Chaft J, Malik S, Mooney M, Abrams JS, Jänne PA, Gandara DR, Ramalingam SS, Vokes EE. ALCHEMIST trials: a golden opportunity to transform outcomes in early-stage non-small cell lung cancer. Clin Cancer Res. 2015 DEC 15; 21 (24): 5439-44. doi: 10.1158/1078-0432. CCR-15-0354.

## 8.0 PATIENT CHARACTERISTICS

Patient Characteristics table includes all registered patients.

| | Total (N=3636) |
|---|---|
| **Age** | |
| N | 3636 |
| Mean (SD) | 66.1 (9.3) |
| Median | 67.0 |
| Q1, Q3 | 60.0, 73.0 |
| Range | (21.0-92.0) |
| | |
| **Gender** | |
| Female | 1973 (54.3%) |
| Male | 1663 (45.7%) |
| | |
| **Race** | |
| White | 3007 (82.7%) |
| Black or African American | 312 (8.6%) |
| Native Hawaiian or Other Pacific Islander | 8 (0.2%) |
| Asian | 159 (4.4%) |
| American Indian or Alaska Native | 11 (0.3%) |
| Not reported: patient refused or not available | 70 (1.9%) |
| Unknown: Patient unsure | 69 (1.9%) |
| | |
| **ECOG PS** | |
| 0 | 1768 (48.6%) |
| 1 | 1868 (51.4%) |
| | |

| | Total (N=3636) |
|---|---|
| **Performance Status Score: Timing** | |
| Preoperative | 110 (3.0%) |
| Pre-adjuvant therapy | 2118 (58.3%) |
| Post-adjuvant therapy | 790 (21.7%) |
| Other | 618 (17.0%) |
| | |
| **Clinical stage non-squamous NSCLC** | |
| IB | 522 (14.4%) |
| II | 1997 (54.9%) |
| IIIA | 1117 (30.7%) |
| | |
| **Primary tumor site** | |
| Not yet available | 71 |
| Bronchus | 6 (0.2%) |
| Left lower lobe lung | 609 (17.1%) |
| Left upper lobe lung | 866 (24.3%) |
| Right lower lobe lung | 710 (19.9%) |
| Right middle lobe lung | 194 (5.4%) |
| Right upper lobe lung | 1114 (31.2%) |
| Other specify | 66 (1.9%) |
| | |
| **Histologic type** | |
| Not yet available | 71 |
| Adenocarcinoma (invasive) | 2614 (73.3%) |
| Adenocarcinoma in situ | 105 (2.9%) |
| Adenosquamous | 75 (2.1%) |
| Carcinoid | 2 (0.1%) |
| Large cell undifferentiated | 19 (0.5%) |
| Large cell with neuroendocrine features | 51 (1.4%) |
| Non-small cell lung cancer NOS | 41 (1.2%) |
| Non-squamous cell carcinoma | 24 (0.7%) |
| Squamous cell carcinoma | 517 (14.5%) |
| Other specify | 117 (3.3%) |
| | |
| **Histologic grade (differentiation)** | |
| Not yet available | 81 |
| Grade I (Well differentiated) | 368 (10.4%) |
| Grade II (Moderately differentiated) | 1651 (46.4%) |
| Grade III (Poorly differentiated) | 1353 (38.1%) |
| Grade IV (Undifferentiated, anaplastic) | 31 (0.9%) |
| GX (Grade cannot be assessed) | 152 (4.3%) |
| | |
| **Maximum diameter of tumor from pathology report (cm)** | |
| N | 3564 |

| | Total (N=3636) |
|---|---|
| Mean (SD) | 4.2 (2.4) |
| Median | 4.0 |
| Q1, Q3 | 2.5, 5.5 |
| Range | (0.0-45.0) |
| | |
| **Pathologic T Stage** | |
| Not yet available | 72 |
| T0 | 2 (0.1%) |
| T1a | 346 (9.7%) |
| T1b | 352 (9.9%) |
| T2a | 1375 (38.6%) |
| T2b | 557 (15.6%) |
| T3 | 848 (23.8%) |
| T4 | 84 (2.4%) |
| | |
| **Pathologic N Stage** | |
| Not yet available | 74 |
| N0 | 1441 (40.5%) |
| N1 | 1318 (37.0%) |
| N2 | 803 (22.5%) |
| | |
| **Clinical M Stage** | |
| Not yet available | 73 |
| M0 | 3561 (99.9%) |
| M1 | 2 (0.1%) |
| | |
| **If Clinical M Stage is M1, Pathologic M Stage: (N=2)** | |
| M1b | 2 (100.0%) |

## 9.0 ADVERSE EVENTS

### 9.1 Adverse Event Summary

Not Applicable

## 10.0 IMBEDDED CORRELATIVES

Not Applicable