Logistics of Alchemist Screening
Trial A151216

Alliance Fall Group Meeting | CRP Breakout Session
November 5, 2015
Presentation Objectives

- To Provide Background and Key Logistics for the Alchemist Screening Trial A151216

- Presenters
  - Colleen Watt – Protocol Coordinator
  - Chelsea Schultz - Data Manager
  - Sumithra Mandrekar – Lead Statistician
  - Shauna Hillman – Statistician
  - Kristen Leraas – Biospecimen Core Resource Rep
  - Miriana Moran – Cancer Genetics formerly Response Genetics Rep
  - Amy Brink – BioMS Rep
ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials)

3 Integrated Trials Testing Targeted Therapy in Early Stage Lung Cancer

● Intent:
  ● Screen patients for EGFR and ALK mutations (A151216)
    ● Enroll ALK or EGFR positive patients in corresponding Adjuvant therapy trial

● Purpose:
  ● ALCHEMIST is studying whether or not treatment based on genotype improves cure rates in early stage (IB-IIIA) NSCLC patients with non-squamous or adeno-squamous tumors that have been completely resected.
ALCHEMIST Structure

ALCHEMIST is an integrated research effort with 3 component trials

- **Screening Trial-A151216**
  - Eligible patients will have their tissue tested for genetic changes in ALK and EGFR.
    - Positive Tissue - they will be referred to one of the treatment trials.
    - Negative Tissue/Not Enrolling in Adjuvant Trial - they will be followed for 5 years.

- **Erlotinib Treatment Trial-A081105**
  - Erlotinib vs. placebo will be evaluated in patients with activating EGFR mutations (prevalence ~ 10-15%) following standard of care adjuvant therapy if applicable

- **Crizotinib Treatment Trial-E4512**
  - Crizotinib vs. placebo will be evaluated in patients harboring the Anaplastic Lymphoma Kinase (ALK) fusion protein (prevalence ~5%) following standard of care adjuvant therapy if applicable

All patients contribute information to the national public resource for research.
ALCHEMIST Screening Trial Eligibility

- **Patient Pre-Registration Eligibility Criteria**
  - Diagnosis of NSCLC (non-squamous or adeno-squamous)
  - Pre-Operative: Clinical stage IB (≥ 4 cm) – IIIA or Post-operative: pathological stage IB (≥ 4 cm) – IIIA
  - Patients with local genotyping are eligible, regardless of the local result.

- **Patient Registration Eligibility Criteria**
  - Complete surgical resection (negative margins)
  - Adequate tissue for EGFR/ALK testing
  - Adequate tissue/blood for NCI CCG genomic research
  - Patients with local genotyping are eligible, regardless of the local result
  - Patients should be registered as follows: within 75 days of surgery when no adjuvant therapy is given, within 165 days after surgery if adjuvant therapy is given, within 225 days after surgery if both chemo and RT are given. (this will be expanded by 2-3 months in an upcoming amendment)
ALCHEMIST Treatment Trial Eligibility

- To open any of the three trials at your site you must obtain IRB approval for all three trials and must open all three trials at the same time.
- Patients must be registered to the ALCHEMIST SCREENING Trial (A151216) prior to randomization to the treatment trials.
- Patients with a tumor positive for translocation or inversion of the ALK gene, based on local or central testing should be further evaluated for participation in Crizotinib Treatment Trial-E4512.
- Patients with a tumor positive for activating EGFR mutation, based on local or central testing should be further evaluated for Erlotinib Treatment Trial-A081105.
- Must have completed standard of care chemotherapy or chemotherapy + radiation therapy if applicable before registering to either Treatment trial E4512 or A081105.
ALCHEMIST Protocol Q & A

Q: Can I submit tissue after pre-registering my patient?
A: No, you must both pre-register and register the patient before submitting tissue.
Q: I have a patient that I want to put on the screening trial but they are not interested in one of the treatment trials, even if they are EGFR or ALK +, should I enroll them on the A151216 only?

A: Patients entering A151216 should be potentially interested in registering to one of the treatment trials. We recognize that patients may change their mind prior to that time.
Q: Do patients need to have adjuvant therapy to enroll?

A: No, even in cases where adjuvant therapy would be standard of care (stage II), eligibility does not require that it be given if that is the decision of the patient and treating physician.
Q: My patient had surgery 1 year ago for his lung cancer. He is now back and has a recurrence. Is this patient eligible?

A: No, A151216 is not for patients with a recurrent lung cancer.
Q: I have a patient with a local EGFR(-) result. These patients are eligible, but why are you interested in them, since they are not likely eligible for the treatment trials?

A: The second primary endpoint of this trial is to perform genomic analysis at the BCR. In addition if a locally negative patient is centrally positive they will be eligible for the corresponding treatment trial.
ALCHEMIST Registration

• Registration for all three trials will occur through OPEN, go to www.allianceforclinicaltrials.org or www.ctsu.org

• If pre-registering pre-operative:
  • Pre-register to A151216
  • Perform surgery
  • Register to A151216
  • Submit tissue to Response Genetics for evaluation
  • If EGFR or ALK +, evaluate for Erlotinib or Crizotinib treatment trials, If a positive local result is already available, a pt. may be registered for the applicable treatment trial immediately

• If pre-registering post-operative:
  • Pre-register and then register to Screening trial A151216
  • Submit tissue to Response Genetics for evaluation
  • If EGFR or ALK +, evaluate for Erlotinib or Crizotinib treatment trials, If a positive local result is already available, a pt. may be registered for the applicable treatment trial immediately
Q: Do I need to register my patient even though I have pre-registered the patient and my pre-registration form says the status is “registered”?
A: This confirmation is for the pre-registration - step 0. A separate registration - step 1 is also required
Q: Why is there both a pre-registration and a registration step?

A: This allows flexibility for enrolling a patient either before or after they have undergone resection. Pre-registering a patient prior to surgery is ideal as it allows preparation of a tissue block as needed per protocol. If pre-registering a patient post surgery, you should pre-register and register at the same time.
ALCHEMIST Data Collection

- Data entry for all three trials will occur via iMedidata Rave
- CRP and site investigators will receive a Rave invitation once their site has IRB approval for all three trials
- A short eLearning will be required prior to access (only required if first time Alliance user of Rave)
- At the time of Pre-registration
  - Complete Screening and Institutional Contact Form
- At the time of Registration
  - All On-Study forms (Background Info, Supporting Documentation, Etc.) will roll out for completion in the baseline folder
  - All forms available via forms packet (Alliance/CTSU Website)
- Follow-up folders will roll out based on the site indicator of registration to either A081105 and E4512 and BCR assessment of sample quality. An indicator will be derived from these fields displaying whether follow-up will be expected for this trial
Baseline Patient Status Form

BCR and RG adequacy assessment will display

Site will indicate “if the pt enrolled in targeted therapy trial”

Site will save the form and follow-up status will display

This form displays information about how patients will be followed
Tissue Adequacy

- If samples are found to be inadequate, the site may submit additional specimens

5.4 Inadequate Submissions

5.4.1 Response Genetics
If the blocks or slides submitted to Response Genetics for ALK/EGFR testing are inadequate, or fail to yield a result, Response Genetics will contact the site requesting an additional submission.

5.4.2 Biospecimen Core Resource
If the remaining tissue from RG or the scrolls submitted by sites are found to be inadequate for genomic analysis the BCR will submit that data to the Data Center. The Data Center will then post this information via RAVE (see Appendix I), after which the site may choose to submit additional tissue for genomic testing. If a site would like to submit additional specimens to BCR for genomic studies, please contact the BCR at 614-355-3589.
Follow-up Patient Status Form

This answer from the Patient Status form along with the tissue adequacy indicators will derive the below field.

Additional derived fields:

<table>
<thead>
<tr>
<th>SMOKING STATUS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline indicator of smoking status <em>(derived)</em></td>
<td></td>
</tr>
<tr>
<td>Has the patient smoked 100 cigarettes (five packs) in their lifetime? <em>(derived field)</em></td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous Visit Smoking Status <em>(derived)</em></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the patient reported quitting smoking on a previous visit? <em>(derived field)</em></td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current smoking status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTRUCTIONS: If the patient was smoking at baseline and has never reported quitting smoking previously, complete the following question</td>
<td></td>
</tr>
<tr>
<td>Has the patient completely quit smoking cigarettes since the last reported smoking status?</td>
<td></td>
</tr>
<tr>
<td><em>(If yes), how long has it been since the patient completely quit smoking cigarettes?</em></td>
<td></td>
</tr>
<tr>
<td><em>(If yes), number of days/weeks/months/years (1 – 99)</em></td>
<td></td>
</tr>
</tbody>
</table>

| Will the patient continue to be followed on ALCHEMIST (A151216) trial? *(derived field)* | Yes |
ALCHEMIST Data Collection

- Pagination may be required on a few of the on-study forms depending on your Rave Set-up parameters (this is not unique to this trial)

- If enrolled on A081105 or E4512, and the patient has a recurrence, go to the A151216 Screening Trial in Rave and the add event section on the subject home page and add the Specimen Submission: Recurrence Tissue form to indicate whether you did or did not submit a sample

- The Specimen Submission: Recurrence Tissue Form will automatically be rolled out if the patient is being followed via the ALCHEMIST screening trial and a recurrence is indicated
You may update your EDC settings by going to “My Profile” and the “edit” icon. Update the number of lines displaying from 20 to 200 so all lines of the log line table display at once.
**ALCHEMIST Data Collection**

- If your lines per page is left at the default of 20 you will need to select “2” or “3” below to get to the second and third page of occupational exposures

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**OCCUPATION REVIEW CHECKLIST**

Did the patient ever have a job as any of the following? (Respond below)

INSTRUCTIONS: Depending on your settings in Rave, this table may be paginated. If the options are available, click on Paginate and select Show All Lines or click on the numeric page numbers at the bottom right corner of the table. If these options are not available, you are already viewing the entire table.

<table>
<thead>
<tr>
<th>#</th>
<th>Occupation/Job</th>
<th>Job held</th>
<th>Number of years job held</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Miner</td>
<td>No</td>
<td>years</td>
</tr>
<tr>
<td>2</td>
<td>Truck driver</td>
<td>No</td>
<td>years</td>
</tr>
<tr>
<td>3</td>
<td>Bus driver</td>
<td>Yes</td>
<td>2 years</td>
</tr>
<tr>
<td>4</td>
<td>Taxi driver</td>
<td>No</td>
<td>years</td>
</tr>
<tr>
<td>5</td>
<td>Heavy equipment operator</td>
<td>No</td>
<td>years</td>
</tr>
<tr>
<td>6</td>
<td>Construction-related occupation</td>
<td>No</td>
<td>years</td>
</tr>
<tr>
<td>7</td>
<td>Vehicle mechanic</td>
<td>No</td>
<td>years</td>
</tr>
<tr>
<td>8</td>
<td>Machinery mechanic</td>
<td>No</td>
<td>years</td>
</tr>
<tr>
<td>9</td>
<td>Dock or warehouse worker</td>
<td>No</td>
<td>years</td>
</tr>
<tr>
<td>10</td>
<td>Ship building or ship repair</td>
<td>No</td>
<td>years</td>
</tr>
</tbody>
</table>
ALCHEMIST Data Collection

- To find the Add Event section navigate to the Rave Subject Home Page and select the Specimen Submission Recurrence Tissue Form and the Add button.
ALCHEMIST Follow-up

- Those not enrolled on A081105 or E4512 are followed for 5 years every 6 months see section 7.3
  - Minimum Follow-up data collected - focused on subsequent therapy and recurrence
- Those enrolled on A081105 or E4512 will be followed via the respective protocol and study calendar
  - A081105 – 10 Years from randomization
  - E4512 – 10 Years from randomization
- A report summarizing the EGFR and ALK results will be sent directly to the sites from Response Genetics
  - Report will be sent by FAX within 14 business days of submission
Data Collection Q & A

Q: Can I send paper CRFs to the research base for data entry?
A: No, data should be entered remotely by the site via iMedidata Rave.
Q: How do I know what data needs to be submitted and when?
A: Consult the Alliance or CTSU website and obtain the Data Submission Guidelines (DSS) and a paper version of the CRFs.
Paper CRFs and DSS Availability
Alliance Website -> Study Page -> Case Report Forms

- Alliance Website
- Study Page
- Case Report Forms

- Protocols
- Data Submission
- Schedule

All CRFs

- Case Report Forms
  - A151216-Allforms-03182014.pdf
  - A151216-DSS-03152015.pdf
  - A151216-DSS-08182014.pdf
  - A151216-OPENrollmentForm-Step0.pdf
  - A151216-OPENrollmentForm-Step1.pdf
Data Collection Q & A

Q: I submitted tissue to RG last week why haven’t I received my results yet?
A: RG will submit results via Fax (using the number provided on the requisition form) within 14 business days of tissue submission.
Introduction to Cancer Genetics (Formerly Response Genetics)

- Response Genetics is a life sciences company engaged in the research and development of clinical diagnostic tests for cancer. They provide validated molecular testing services to physicians and their patients, enabling personalized cancer treatment based on genetic analysis.

- Tissue is sent to RG to centrally genotype for EGFR mutations and ALK rearrangements.
Introduction to the BCR

- The Biospecimen Core Resource (BCR) is a centralized laboratory that reviews and processes blood and tissue samples for cancer genomics projects.
- Tissue is sent to the BCR to facilitate clinically annotated advanced genomic analysis in concert with the NCI Center for Cancer Genomics.
ALCHEMIST Specimen Shipment

- Submit to Response Genetics
  - Tissue Specimens for ALK/EGFR analysis
  - Pathology report
- Submit to NCI CCG Biospecimen Core Resource (BCR)
  - Sites submitting blocks to Response Genetics do not need to submit tissue to the BCR. Sites submitting unstained slides to RG will submit scrolls and a H&E stained slide to the BCR
  - Blood Specimens will be submitted for all patients to BCR
  - Recurrence Biopsies
  - Shipments to BCR only occur Monday – Thursday (No Saturday Delivery)

- For samples shipped to RG, include the Clinical Assay Request form (prints with BioMS shipping manifest)

*See Section 5.4.1 & 5.4.2 for shipping addresses*
Clinical Assay Request Form
(EGFR and ALK)

Patient Initials (First, Middle, Last): ____________

PATIENT ALCHEMIST (A151216) ID: ____________

Patient DOB (MM/DD/YYYY): ___/___/____

Surgery Date (MM/DD/YYYY): ___/___/____

CRA Ordering Text: RESULTS WILL BE COMMUNICATED TO THIS INDIVIDUAL [please print]:

Name (First, Last): __________________________ Institution: __________________________

Order Physician (First, Last): __________________________ CTEP Institution Number: __________________________

Address:

Street

City __________________________ State __________ Zip __________________________

Phone: (__), ________ Fax: (__), ________ Email: __________________________

Submission Date (MM/DD/YYYY): ___/___/____

<table>
<thead>
<tr>
<th>Check One</th>
<th>Specimen type (enter number of specimens)</th>
<th>Surgical Pathology Case Number</th>
<th>Block Letter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formalin fixed, paraffin embedded tumor tissue block (created for study use)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 H/E stained slide from submitted block</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Formalin fixed, paraffin embedded tumor tissue block (from clinical pathology department)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 H/E stained slide from submitted block</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5, 10 micron tumor tissue sections mounted to charged slides</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3, 5 micron tumor tissue sections mounted to charged slides</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 H/E stained slide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please ship this request form with BioMS packing slip and the specimen to:
Response Genetics, Inc.
Pharmaceutical Services
1640 Marengo Street, 6th Floor
Los Angeles, California 90033
Steps for creating and shipping scrolls:
1. Measure length and width (in mm) of tissue specimen contained within paraffin block.
2. Double click on excel table below to open editing function.
3. Enter tumor length and width values measured in step 1.
4. Number of 10 micron scrolls required is shown in yellow.
5. Put scrolls in tube for shipping (Eppendorf or cryovial)

6. Ship immediately to the BCR ambient (please contact for airbill)

Examples for measuring tumor area are on next slide.

Contact Kristen Leraas at the NCH BCR with more questions:
kristen.leraas@nationwidechildrens.org
614-355-3589
To calculate the number of 10uM thick scrolls:

\[ \frac{12}{0.01 \times L \times W} \]

**Example #1**
- Length = 12mm
- Width = 4mm

**Example #2**
- Length = 8mm
- Width = 8mm

**Example #1 Answer** – 
\[ \frac{12}{0.01 \times 12 \times 4} = 25 \text{ Scrolls} \]

**Example #2 Answer** – 
\[ \frac{12}{0.01 \times 8 \times 8} = 19 \text{ Scrolls} \]

Contact Kristen Leraas at the NCH BCR with more questions:
kristen.leraas@nationwidechildrens.org
614-355-3589
Specimen Shipment Q&A

Q: Do you provide kits?
A: No, but we will provide airbills for specimens coming to the BCR.

Q: How are we informed if a patient fails at the BCR?
A: There is no formal notification. You may log into RAVE and review the adequacy form submitted by the BCR. You may provide additional specimen if possible in attempt to salvage the case.
Specimen Shipment Q&A

Q: Should we ship ambient?
A: Yes, unless the blood has been frozen then ship on dry ice.

Q: What if my site cannot release the block?
A: Please refer to slide 32 and 33 for creating and shipping scrolls.
Specimen Shipment Q&A

Q: Can samples be returned?
A: Yes. The BCR will need written email notification and for the TSS to send an airbill (or FedEx account) for shipping.
Biospecimen Management System-BioMS
Introduction to BioMS

- Requires a valid CTEP-IAM (CTSU) username and password.

- Logging Biospecimen in BioMS is a **pre-requisite** for shipping to any Alliance biorepository or assay lab associated to an Alliance trial.

- The certified browsers for BioMs are IE 11.0, Mozilla Firefox 30.0 and if you have a Mac, Safari 7.0.
ALCHEMIST Trial A151216

- Special Note: For the ALCHEMIST Trial there is a mandatory form in BioMS that must be completed. The application will not allow the user to advance to the shipping page until this form has been completed. Please note that if you are not using one of the certified browsers listed, you will not be able to access the form.

Mandatory form. Click the clipboard icon.
BioMS User Support

- Visit our webpage page at http://tinyurl.com/alliance-bioms
- Email us at BioMShelp@bmi.wustl.edu
- Call us toll free at 1(855) 552-4667
BioMS Q&A

Q. My site is not allowed to release the block so I have slides and curls to send but I cannot select them in BioMS, what do I do?

A. In order to send the Alternate specimens (Unstained slides, Tissue Scrolls), the CRA must first indicate that the Fixed Tissue Block will not be collected. This is done by selecting the "did not collect" Icon . Upon clicking the icon a pop-up window will open requesting the CRA to select a reason. CRAs can select the option "Cannot Release Block", then click Save. Once this is done the screen will refresh and the alternate specimens will be activated for collection
Q. What is meant by "Collection Date"? Is this the day the patient had surgery, or the day I received the specimen from my pathology department?

A. The "Collection Date" is the date that the procedure was performed. Please note that when a specimen is selected the current date and time are populated in this field. Please be sure to adjust the date to the correct date.
BioMS Q&A

Q. When I click on the clipboard icon with the ! there is nothing there and the same is true when I click the "Not Collected" icon, why is this?

A. The CRA is likely not using a certified BioMS browser. If your site will not allow a certified browser, please contact the BioMS Help Desk and information can be entered for you.
BioMS Q&A

Search for a patient(s)
Enter Patient ID, Patient initials or Study ID and click search to search for finding patient registrations. E.g. Patient ID = 10 or Patient initials = S V (Last name, first name middle name) or Study ID = 10. Wildcard (%) is automatically appended to the end of search criteria.

PATIENT SEARCH

Patient ID [ ] Start typing here Search

CRA cannot see drop down selection in IE 8

Search for a patient(s)
Enter Patient ID, Patient initials or Study ID and click search to search for finding patient registrations. E.g. Patient ID = 10 or Patient initials = S V (Last name, first name middle name) or Study ID = 10. Wildcard (%) is automatically appended to the end of search criteria.

PATIENT SEARCH

Patient ID [ ] Start typing here Search

Firefox
### BioMS Q&A

#### IE 8- Cannot read epochs, cannot see Save and Go to shipments

<table>
<thead>
<tr>
<th>Collected</th>
<th>Study</th>
<th>Specimen expected</th>
<th>Quantity</th>
<th>Collection date</th>
<th>Status</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>20ml ACD Whole Blood (2x10ml)</strong></td>
<td>20.0 ml</td>
<td></td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>20ml EDTA Whole Blood (2x10ml)</strong></td>
<td>20.0 ml</td>
<td></td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>5ml No Additive Serum (5x0.5ml)</strong></td>
<td>5.0 ml</td>
<td></td>
<td>Pending</td>
<td></td>
</tr>
</tbody>
</table>

#### Firefox

<table>
<thead>
<tr>
<th>Collected</th>
<th>Study</th>
<th>Specimen expected</th>
<th>Quantity</th>
<th>Collection date</th>
<th>Status</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>20ml ACD Whole Blood (2x10ml)</strong></td>
<td>20.0 ml</td>
<td></td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>20ml EDTA Whole Blood (2x10ml)</strong></td>
<td>20.0 ml</td>
<td></td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>5ml No Additive Serum (5x0.5ml)</strong></td>
<td>5.0 ml</td>
<td></td>
<td>Pending</td>
<td></td>
</tr>
</tbody>
</table>
Take Home Message

- To open the trial you must obtain IRB approval for all three trials (A151216, A081105, E4512)
- Either 2 or 3 registrations will occur for participation in this trial
- All patients will be followed for at least 5 years regardless of EGFR and ALK status with the exception of those with inadequate samples for genomic testing
- Required protocol samples will be logged in BioMS and sent to either Response Genetics or the BCR
- Data entry will occur in iMedidata Rave
- Navigation for this trial will be driven by:
  - Site entered data
  - Specimen adequacy as provided by the BCR
  - Follow-up status will be derived and displayed within Rave
The Future of ALCHEMIST Screening Trial

ALCHEMIST is designed to accommodate evolving clinical science and research opportunities. Evaluation of other targeted therapies could be added to the research effort as new and promising therapies emerge.
EA5142
Adjuvant Nivolumab in Resected Lung Cancers (ANVIL) – A Randomized Phase III Study of Nivolumab After Surgical Resection and Adjuvant Chemotherapy in Non-Small Cell Lung Cancers

Sumithra Mandrekar
Faculty Statistician
Nivolumab vs docetaxel

Overall Survival

Non-squamous

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 292</td>
<td>292</td>
<td>290</td>
</tr>
</tbody>
</table>

OS (%)

- 1-yr OS rate = 51%
- 1-yr OS rate = 39%

Time (months)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>146</td>
<td>111</td>
</tr>
<tr>
<td>18</td>
<td>123</td>
<td>88</td>
</tr>
<tr>
<td>24</td>
<td>62</td>
<td>34</td>
</tr>
<tr>
<td>27</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

Squamous

Overall Survival

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 135</td>
<td>135</td>
<td>137</td>
</tr>
</tbody>
</table>

OS (%)

- 1-yr OS rate = 42%
- 1-yr OS rate = 24%

Time (months)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>86</td>
<td>113</td>
</tr>
<tr>
<td>18</td>
<td>69</td>
<td>30</td>
</tr>
<tr>
<td>24</td>
<td>69</td>
<td>14</td>
</tr>
</tbody>
</table>

Paz-Ares, ASCO 2015
Spigel, ASCO 2015
Toxicities (N=535)

- Most patients have little to no severe toxicity
- Any type of –itis is possible
- Most common (Low grade)
  - Dermatitis
  - Pruritus
  - Nausea
  - Diarrhea
  - Thyroiditis (often subclinical and leads to burn out)
  - Fatigue
  - Arthralgias
- Rare but serious (Grade 3 or 4)
  - Colitis (1.1%)
  - Hepatitis (<1%)
  - Pneumonitis (1.3%)
  - Infusion reaction (<1%)
  - Adrenal insufficiency (<1%)
EA5142 Schema

Eligibility
• Patient registered to ALCHEMIST screening trial (A151216)
• EGFR/ALK wildtype (if non-squamous)
• No contraindication to nivolumab

Stratification
• Stage (IB/IIA vs. IIB/IIIA)\(^1\)
• Histology (squamous/non-squamous)\(^2\)
• Adjuvant Chemotherapy for Lung Cancer (none/chemotherapy/chemotherapy + radiation)
• PD-L1 Status (+ vs. -/non-evaluable)\(^3\)

Nivolumab 240mg IV q2 weeks for up to 1 year\(^4\)

Observation per standard of care

Cycle = 2 weeks (14 days)
Accrual Goal = 714 patients

1. If Stage 1B, then tumor must be ≥ 4cm
2. Adenosquamous should be grouped as non-squamous
3. PD-L1+ is defined as ≥ 1% by IHC
4. Maximum number of doses is 26
5. Patients will be followed for recurrence and survival for 10 years
Statistical Plan

- Co-primary endpoints of DFS and OS
  - OS: 81% power to detect a 30% reduction in the OS hazard rate
  - DFS: 82.5% power to detect a 33% reduction in DFS hazard rate
- Sample size 714 patients
  - Overall one-sided type I error rate 0.025 for the trial
- Assuming accrual of 21 patients per month (similar to E1505), study duration is ~6.4 years
Questions?
ALCHEMIST Trial Current Status as of Oct 12, 2015

Figure 1: Accrual Graph: Pre-registered (472) and Registered (446)
ALCHEMIST Trial Current Status as of Oct 12, 2015

- 205 sites have registered at least 1 pt
- 472 pre-registered with 446 registered
- 82 ECOG, 57 NRG, 45 SWOG, 262 Alliance
- Currently enrolling ~ 60 a month
- Target accrual 100 a month
Identifying Barriers to Participation on Alchemist Trial