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

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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.

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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 Trail - 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.

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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)

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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

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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.

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ALCHEMIST Protocol Q & A

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.

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ALCHEMIST Protocol Q & A

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.

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ALCHEMIST Protocol Q & A

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.

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ALCHEMIST Protocol Q & A

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.

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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

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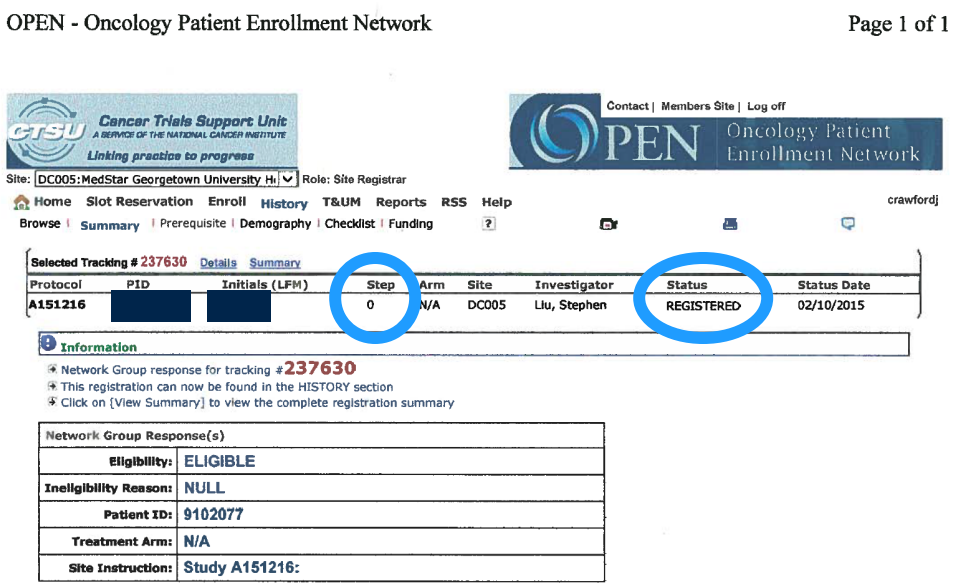
ALCHEMIST Registration Q & A

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



OPEN - Oncology Patient Enrollment Network Page 1 of 1

Cancer Trials Support Unit — A SERVICE OF THE NATIONAL CANCER INSTITUTE — Linking practice to progress

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OPEN Oncology Patient Enrollment Network

Site: DC005:MedStar Georgetown University Ho Role: Site Registrar

Home Slot Reservation Enroll History T&UM Reports RSS Help crawfordj

Browse | Summary | Prerequisite | Demography | Checklist | Funding

Selected Tracking # 237630 Details Summary

Protocol	PID	Initials (LFM)	Step	Arm	Site	Investigator	Status	Status Date
A151216	[redacted]	[redacted]	0	N/A	DC005	Liu, Stephen	REGISTERED	02/10/2015

Information

- Network Group response for tracking #237630
- This registration can now be found in the HISTORY section
- Click on [View Summary] to view the complete registration summary

Network Group Response(s)	
Eligibility:	ELIGIBLE
Ineligibility Reason:	NULL
Patient ID:	9102077
Treatment Arm:	N/A
Site Instruction:	Study A151216:

ALCHEMIST Registration Q & A

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

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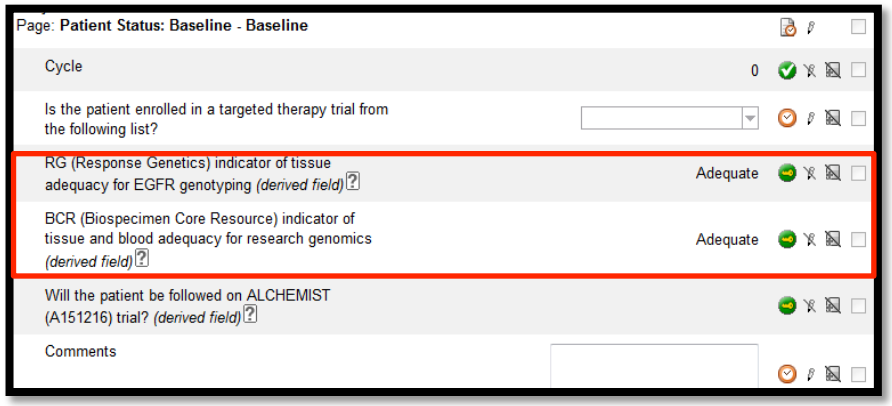
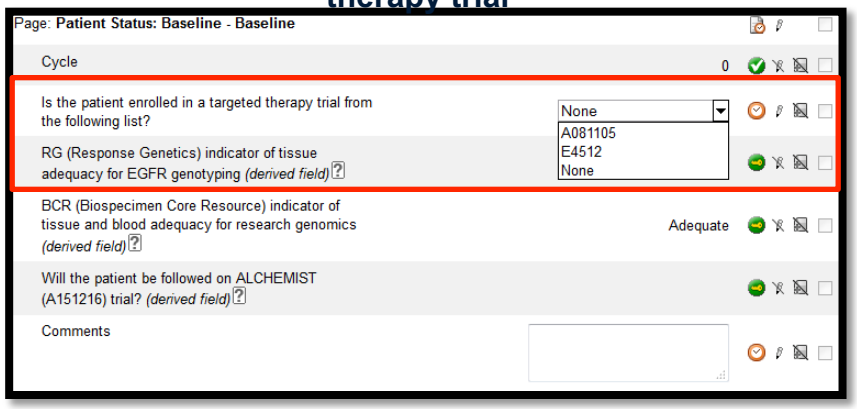
Baseline Patient Status Form

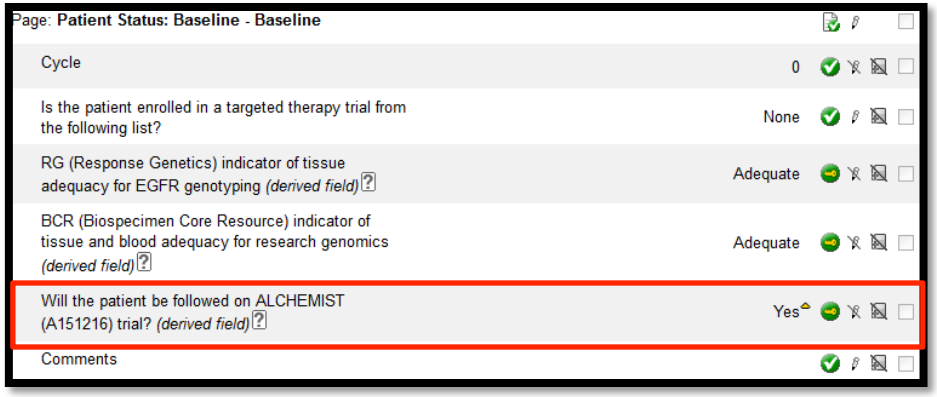
BCR and RG adequacy assessment will display



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

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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.

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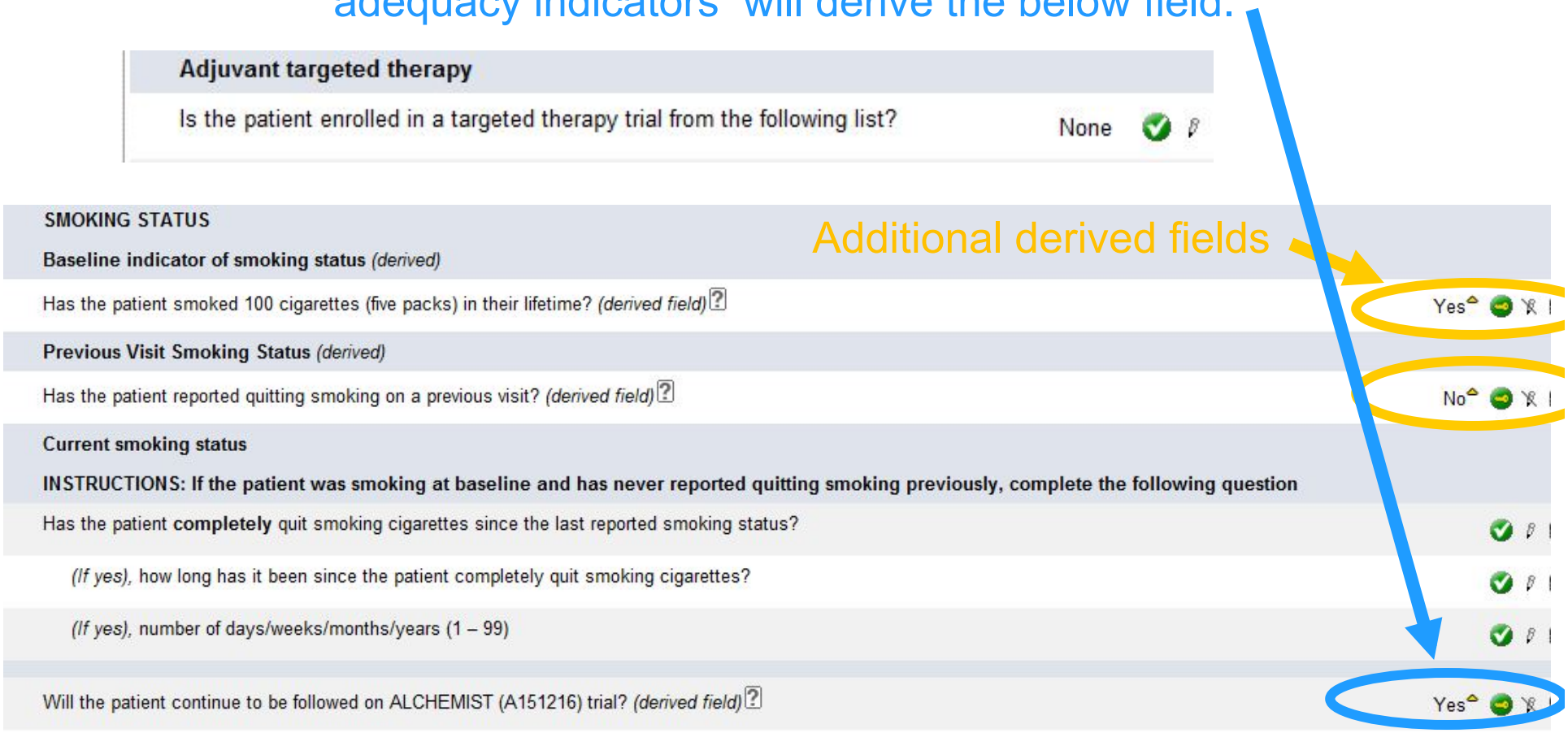
Follow-up Patient Status Form

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



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

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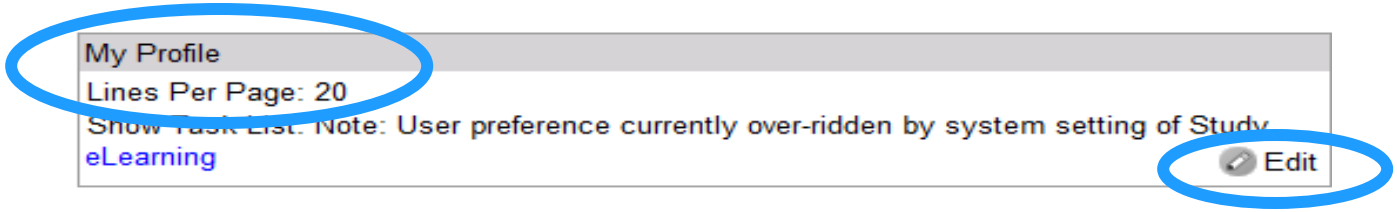
ALCHEMIST Data Collection

- 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



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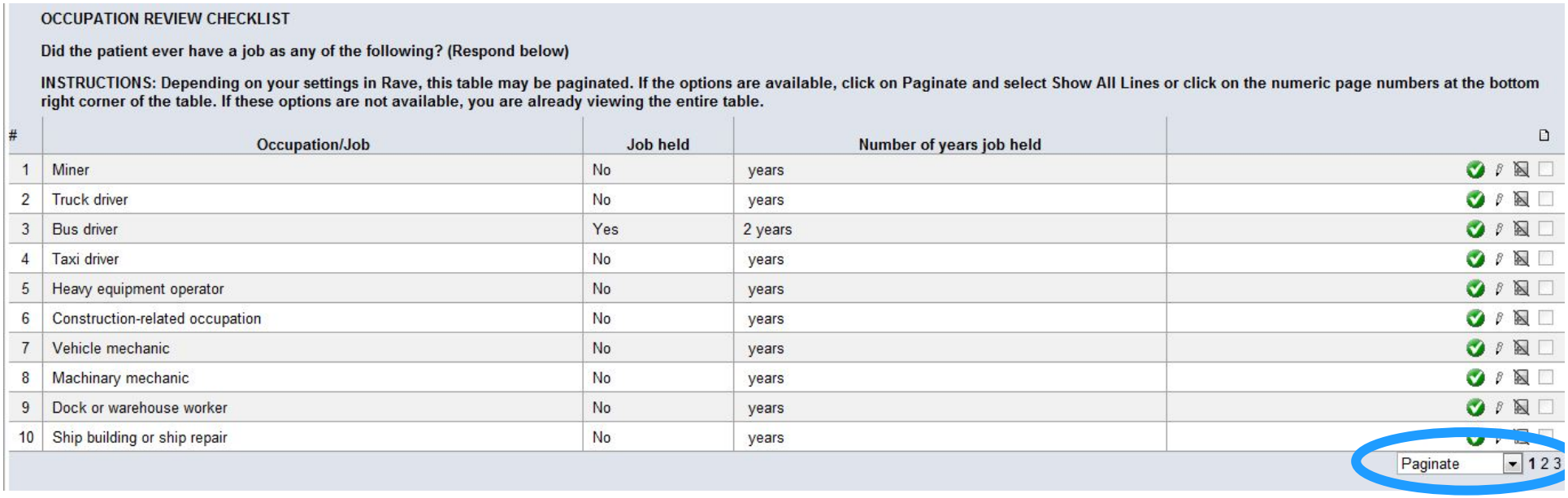
ALCHEMIST Data Collection

- 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



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.

#	Occupation/Job	Job held	Number of years job held
1	Miner	No	years
2	Truck driver	No	years
3	Bus driver	Yes	2 years
4	Taxi driver	No	years
5	Heavy equipment operator	No	years
6	Construction-related occupation	No	years
7	Vehicle mechanic	No	years
8	Machinary mechanic	No	years
9	Dock or warehouse worker	No	years
10	Ship building or ship repair	No	years

Paginate 1 2 3

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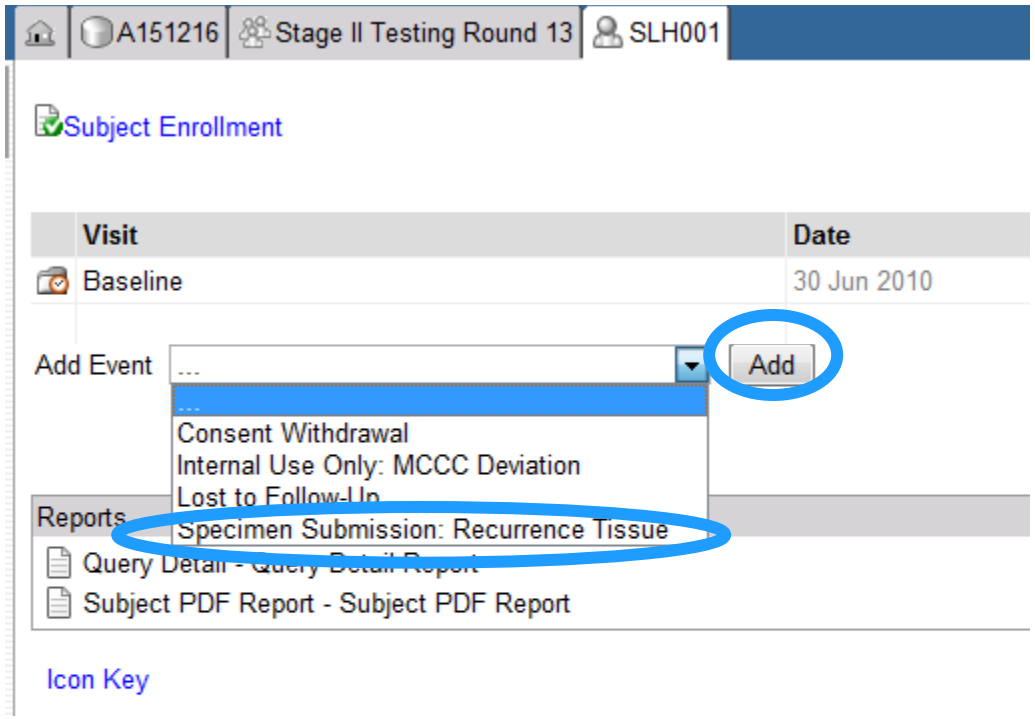
ALCHEMIST Data Collection

- 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



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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

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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.

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Data Collection Q & A

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.

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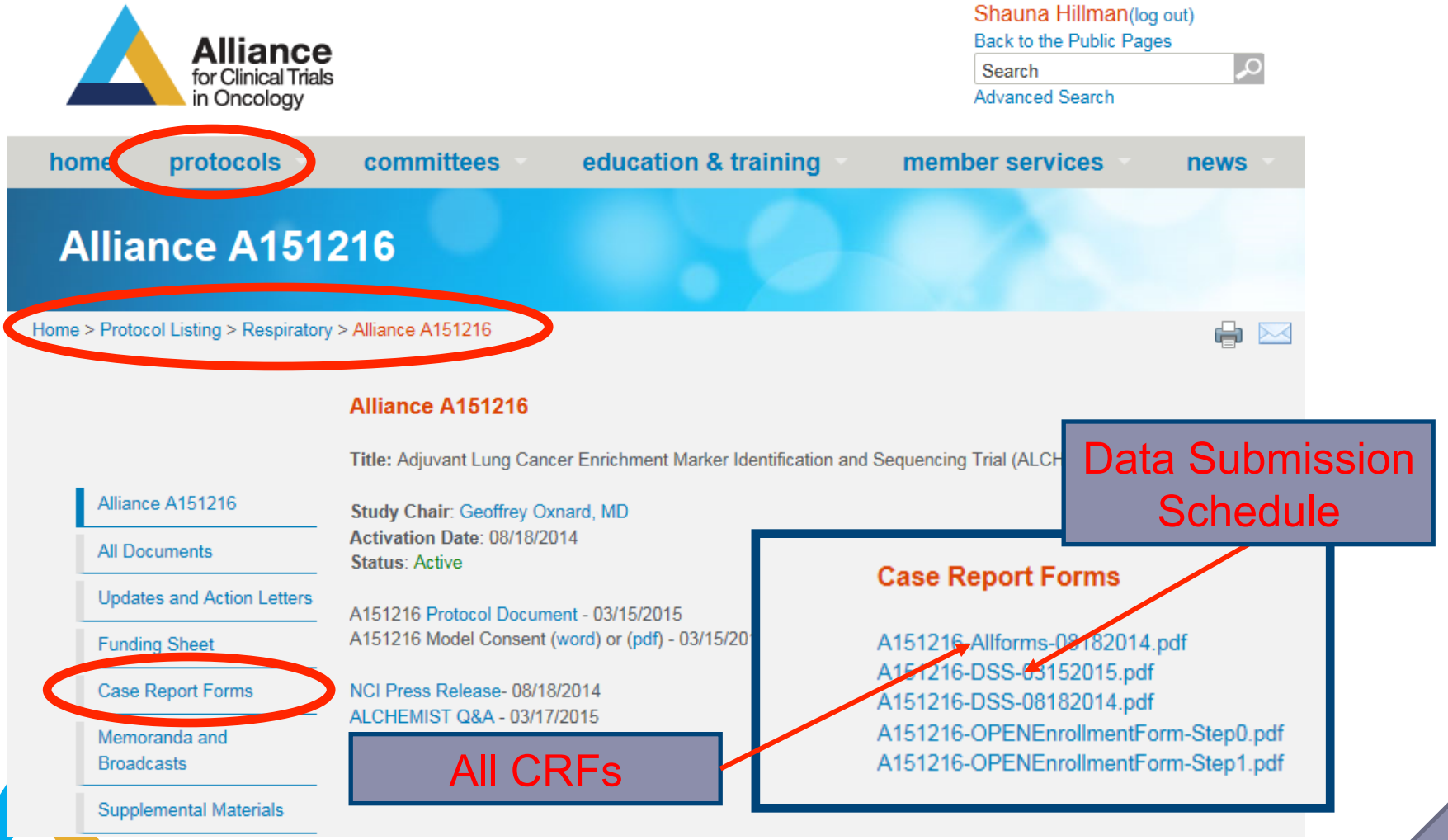
Paper CRFs and DSS Availability

Alliance Website -> Study Page -> Case Report Forms



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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.

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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

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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

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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 Test- 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):_____/_____/_____

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

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 th *"Double Click" below to activate table* ill)

Scroll Calculator					
Enter tissue area width:	12	mm			
Enter tissue area length:	12	mm			
Enter scroll thickness:	10	microns	(please submit 10 micron scrolls)		
How much volume of tissue do you need?			12	mm3	
Cut this many scrolls >>>	8				

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

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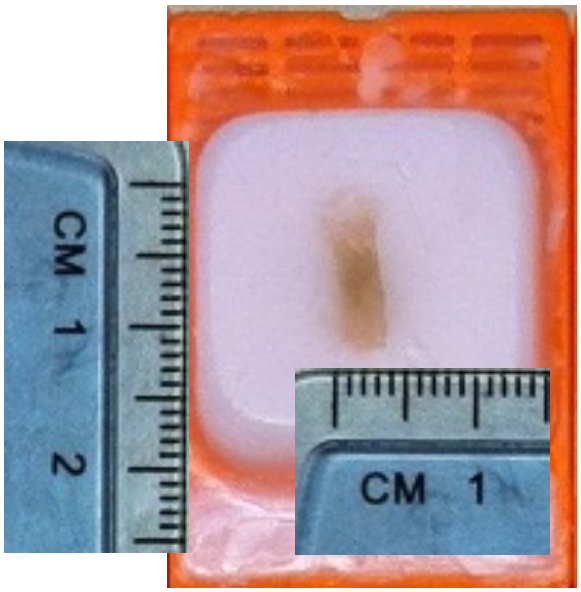
Example #1

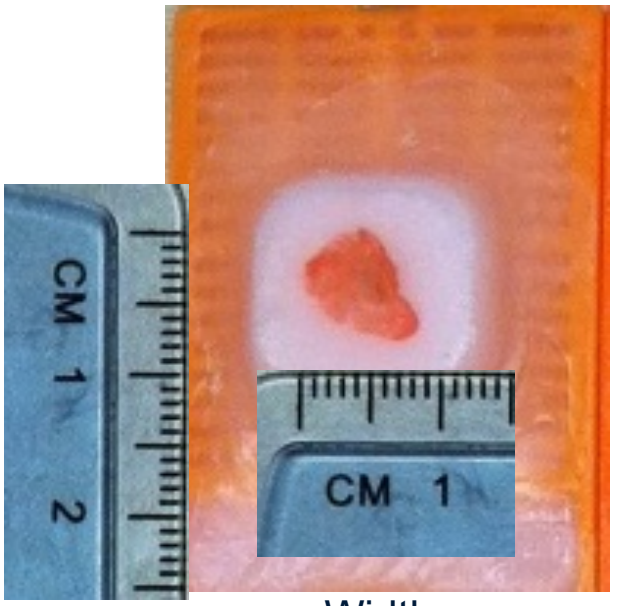
Length
=12mm



Width
=4mm

Example #2

Length
=8mm



Width
=8mm

To calculate the number of 10uM thick scrolls…. $= 12 / (0.01 * L * W)$

- L = **Total surface area to be cut (mm^3)**
- 0.01 = **Scroll thickness (mm)**
- L = **Tissue Length (mm)**
- W = **Tissue Width (mm)**

Example #1 Answer –
12 / (0.01 * *12* * *4*) = 25 Scrolls

Example #2 Answer –
12 / (0.01 * *8* * *8*) = 19 Scrolls

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

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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.

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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.

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Biospecimen Management System-BioMS

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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.

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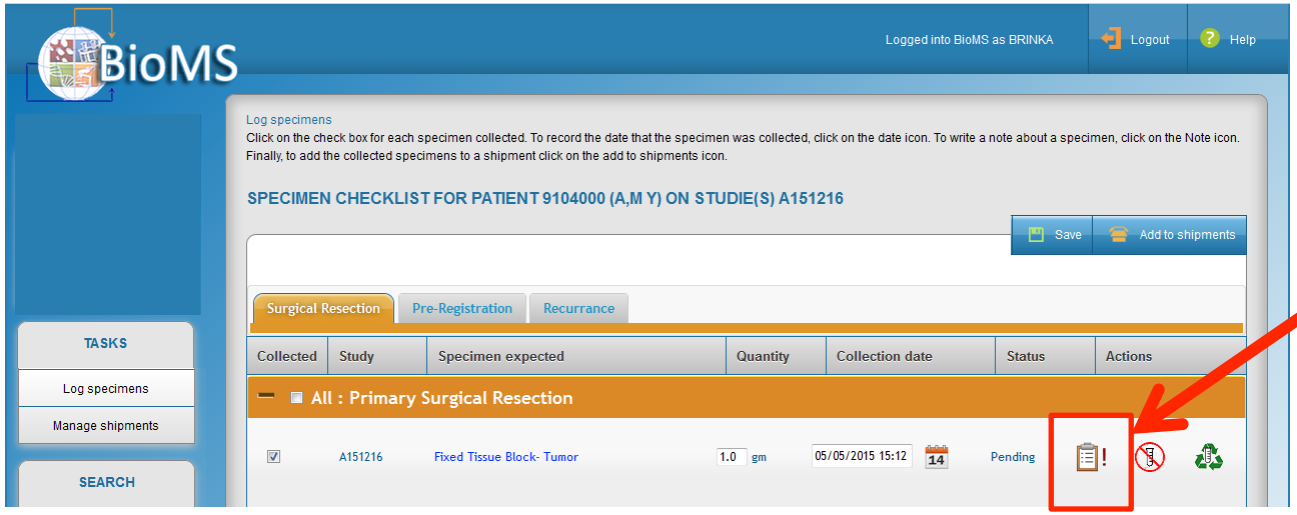
ALCHEMIST Trial A151216

- 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 not 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

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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

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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

BioMS Q&A

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?

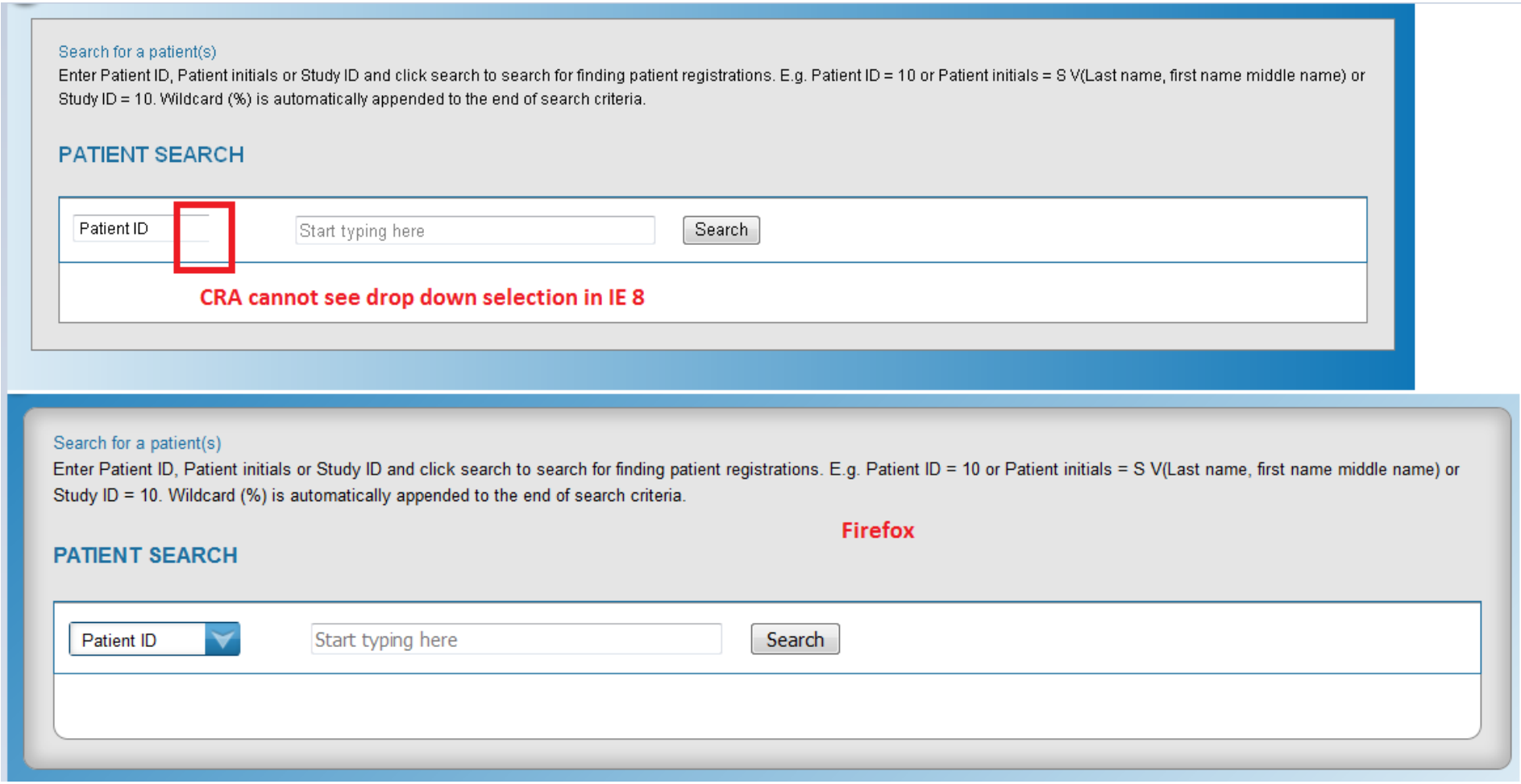
A. The "Collection Date" is the date that the procedure was performed. Please note that when a specimen is selected the current date and time are populated in this field. Please be sure to adjust the date to the correct date.

BioMS Q&A

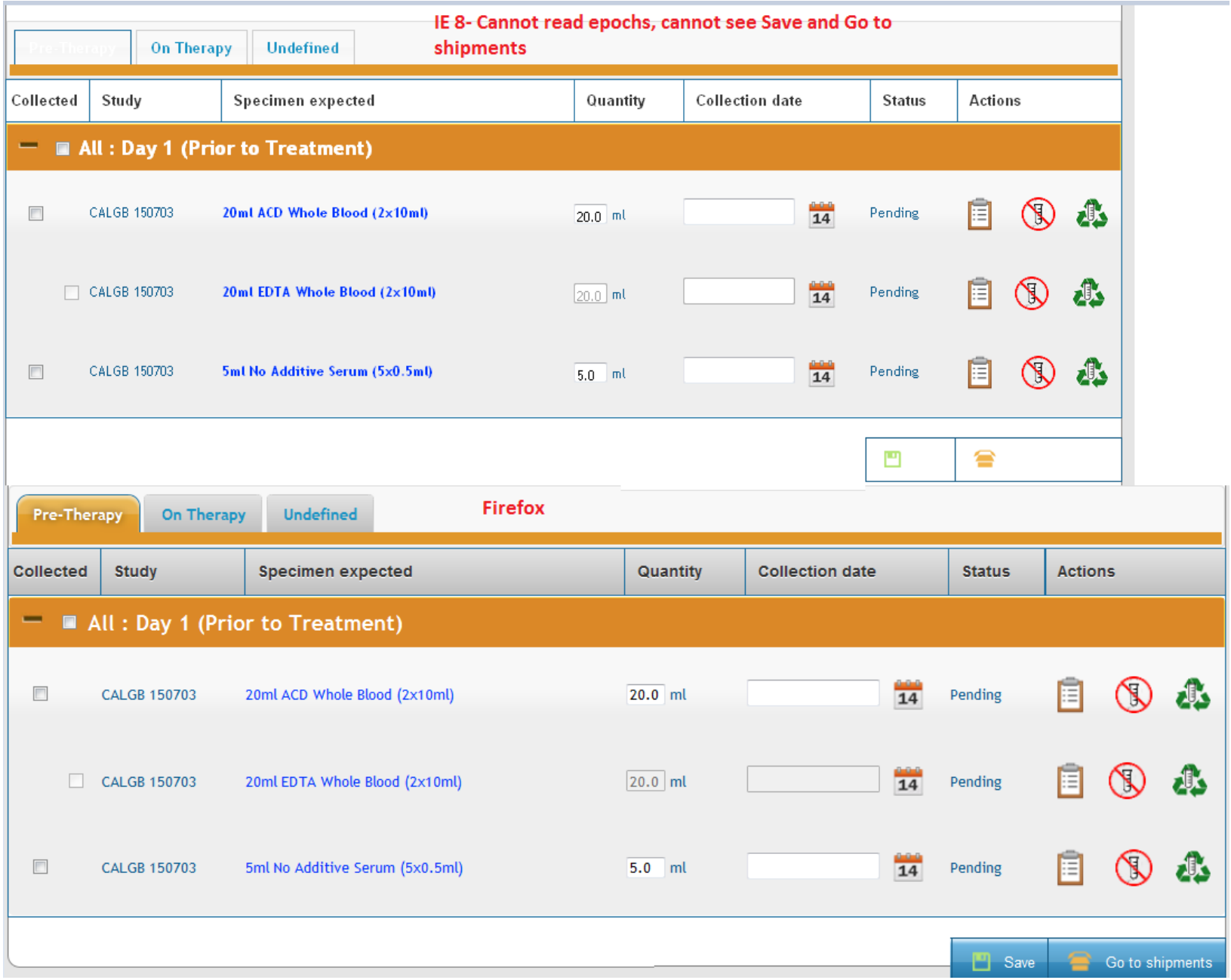
Q. When I click on the clip board icon with the ! there is nothing there and the same is true when I click the "Not Collected" icon, why is this?

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.
Firefox
PATIENT SEARCH
Patient ID
Start typing here
Search

BioMS Q&A


IE 8- Cannot read epochs, cannot see Save and Go to shipments
Pre-Therapy
On Therapy
Undefined
Collected
Study
Specimen expected
Quantity
Collection date
Status
Actions
All : Day 1 (Prior to Treatment)
CALGB 150703
20ml ACD Whole Blood (2x10ml)
20.0 ml
Pending
CALGB 150703
20ml EDTA Whole Blood (2x10ml)
20.0 ml
Pending
CALGB 150703
5ml No Additive Serum (5x0.5ml)
5.0 ml
Pending
Firefox
Pre-Therapy
On Therapy
Undefined
Collected
Study
Specimen expected
Quantity
Collection date
Status
Actions
All : Day 1 (Prior to Treatment)
CALGB 150703
20ml ACD Whole Blood (2x10ml)
20.0 ml
Pending
CALGB 150703
20ml EDTA Whole Blood (2x10ml)
20.0 ml
Pending
CALGB 150703
5ml No Additive Serum (5x0.5ml)
5.0 ml
Pending
Save
Go to shipments

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

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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.

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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

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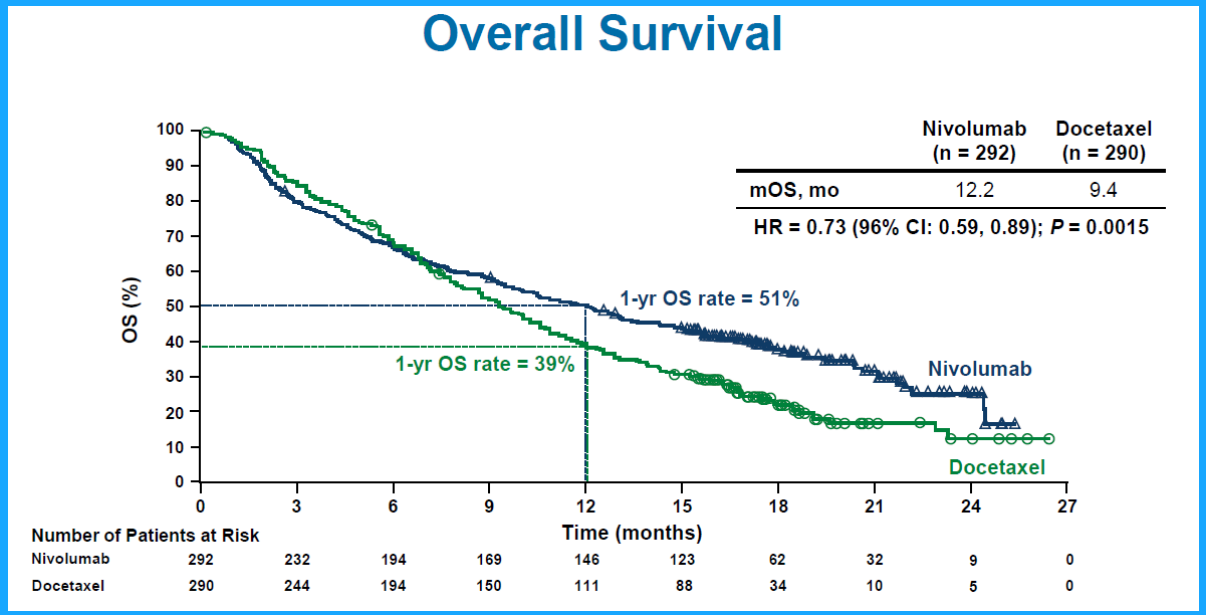
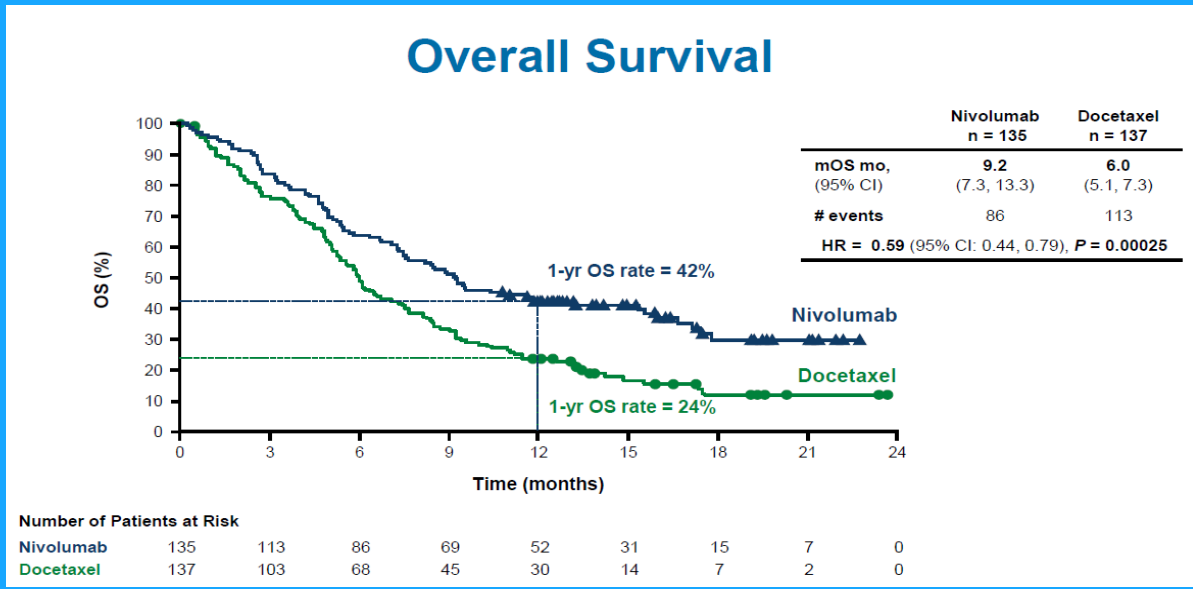
Nivolumab vs docetaxel

Non-squamous



Squamous

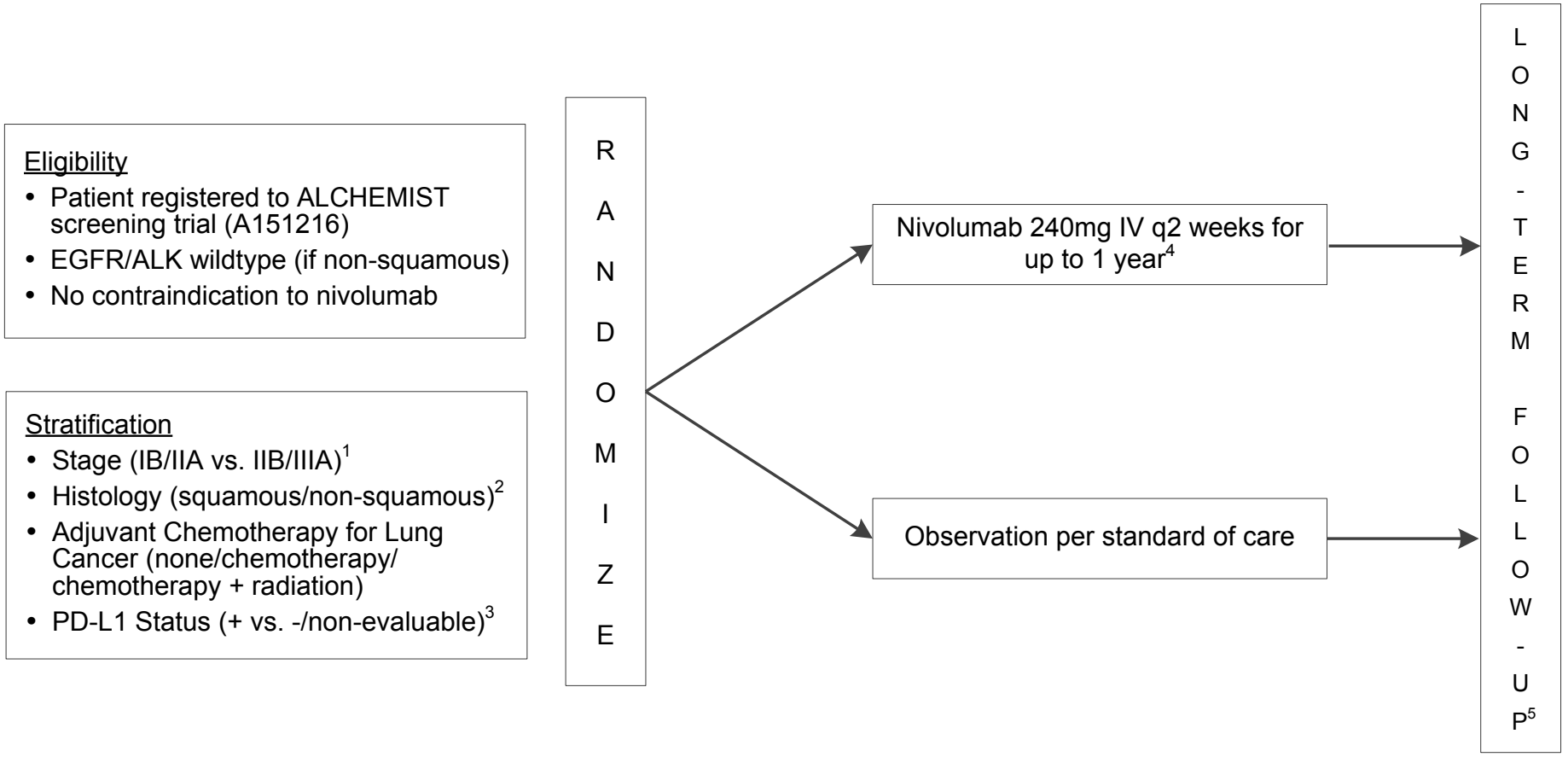


Paz-Ares, ASCO 2015
Spigel, ASCO 2015

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



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?

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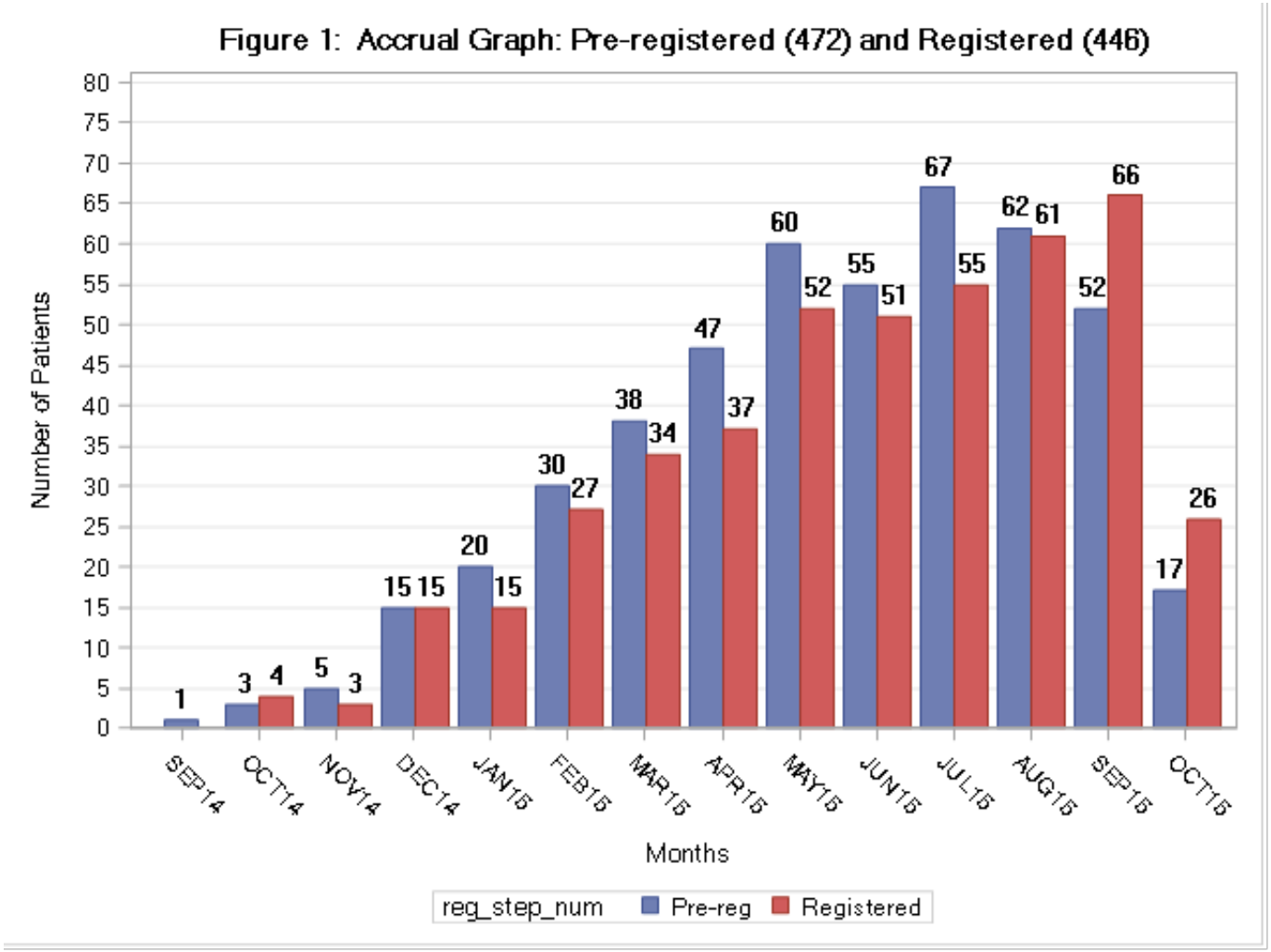
ALCHEMIST Trial Current Status as of Oct 12, 2015



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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

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Identifying Barriers to Participation on Alchemist Trial

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