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Activation Date March 25, 2015

SWOG

A RANDOMIZED PHASE II TRIAL OF AFATINIB PLUS CETUXIMAB VERSUS AFATINIB ALONE IN TREATMENT-NAÏVE PATIENTS WITH ADVANCED, EGFR MUTATION POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC) (BI 1200.124)

NCT#02438722

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AGENTS:

SWOG-held IND agents:
Afatinib (BIBW2992) (Gilotrif) (NSC 750691) (IND-125069)
Cetuximab (IMC-C225) (Erbitux®) (NSC-714692) (IND-125069)

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Submit study data
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	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 section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx

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.

For patient eligibility questions, contact the SWOG Statistics and Data Operations Center by phone or email:

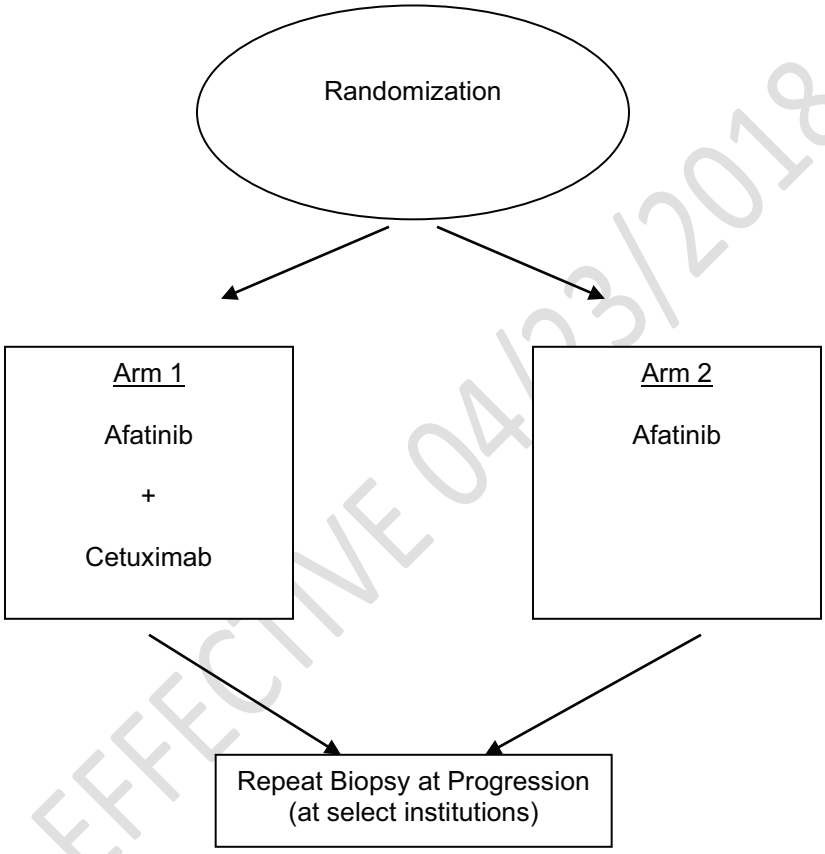
206-652-2267
lungquestion@crab.org

For treatment or toxicity related questions, contact Dr. Goldberg or Dr. Lilenbaum.

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 Website is located at https://www.ctsu.org.

SCHEMA



1.0 OBJECTIVES

1.1 Primary Objective

a. To compare progression-free survival between patients randomized to afatinib in combination with cetuximab versus afatinib alone as first-line treatment for EGFR-mutant NSCLC.

1.2 Secondary Objectives

a. To evaluate the overall response rate (confirmed and unconfirmed, complete and partial responses) in the subset of patients with measurable disease treated with afatinib plus cetuximab compared to afatinib alone.

b. To assess the safety of each treatment arm when used in the first-line setting.

c. To compare time to treatment failure and time to treatment discontinuation (as defined in Sections 10.5 and 10.6) between randomized to afatinib in combination with cetuximab versus afatinib alone.

d. To compare overall survival (OS) between the arms.

1.3 Translational Objectives

a. To investigate the molecular mechanisms that confer benefit from afatinib and afatinib plus cetuximab by evaluating whether the presence of *de novo EGFR T790M* mutation or other molecular alterations in the pre-treatment tumor influence the clinical outcomes

b. To quantitatively assess whether the ratio of sensitizing *EGFR* (*EGFR*s) mutation to *EGFR T790M* influences outcome and is altered during treatment.

c. To evaluate the frequency of known mechanisms of resistance to EGFR-directed therapies in the context of afatinib plus cetuximab and afatinib alone treatment.

d. To identify potential novel predictors of benefit to afatinib plus cetuximab.

e. To identify potential new mechanisms of resistance to EGFR-directed therapies.

f. To establish patient-derived xenografts (PDXs) from a subset of patients by re-biopsy at the time of progressive disease for drug testing and genomic analysis.

g. To assess whether circulating tumor markers can be used as indicators of sensitivity and resistance to afatinib plus cetuximab and afatinib alone.

h. To determine whether the levels of EGFR protein by immunohistochemistry predict for benefit to afatinib plus cetuximab and afatinib alone.

2.0 BACKGROUND

EGFR Mutation Positive NSCLC

NSCLC is the leading cause of cancer-related death worldwide, and results in over 160,000 deaths in the United States per year. In patients with advanced or metastatic disease, platinum-based chemotherapy had been the mainstay of management with a response rate and median overall survival of approximately 30% and 12 months, respectively. Over the past decade,

identification of oncogenic drivers of NSCLC and targeted therapies that inhibit these drivers have revolutionized the way in which lung cancer is treated. Approximately 15% of all patients with NSCLC harbor a mutation in the Epidermal Growth Factor Receptor (EGFR) gene of the tumor. *(1,2,3)* Most of these mutations affect small regions of the gene within exons 18 to 21 that code for the EGFR tyrosine kinase domain. The most common mutations result in an in-frame deletion in exon 19 and a point mutation resulting in an amino acid substitution at codon 858 (L858R) in exon 21. There are currently two classes of EGFR-targeted agents with distinct mechanisms of action: monoclonal antibodies against the extracellular domain of this receptor (i.e. cetuximab), and small molecule tyrosine kinase inhibitors (TKIs, i.e. erlotinib, gefitinib, and afatinib) which act as ATP analogues and compete for the tyrosine kinase catalytic site thus interfering with inhibition of receptor activation. EGFR TKIs have revolutionized the way in which NSCLC is treated, as they are extremely effective in treating patients with EGFR-mutated cancers, especially compared to chemotherapy.

First-generation EGFR Tyrosine Kinase Inhibitors (TKIs)

Several large, randomized trials have now shown the benefit of treating patients whose tumor harbors an *EGFR* mutation with gefitinib or erlotinib in the first-line setting compared to chemotherapy. *(4,5,6,7)* Although there is clearly an advantage to the use of EGFR TKIs as upfront treatment of *EGFR*-mutant NSCLC compared to chemotherapy, resistance typically develops after a median of about one year. The most common molecular characteristic found in tumors at the time of resistance to EGFR TKIs, observed in 50-60% of cases, is acquisition of a secondary mutation in *EGFR*, the T790M mutation that increases the affinity of the kinase for ATP and therefore alters the ability of gefitinib or erlotinib to bind in the ATP-binding site of the receptor. *(8)* While multiple other mechanisms of EGFR TKI resistance have also been described, including *MET* and *HER2* amplification, no therapeutic strategies to overcome resistance have been approved. *(9)*

Afatinib in EGFR Mutation Positive NSCLC

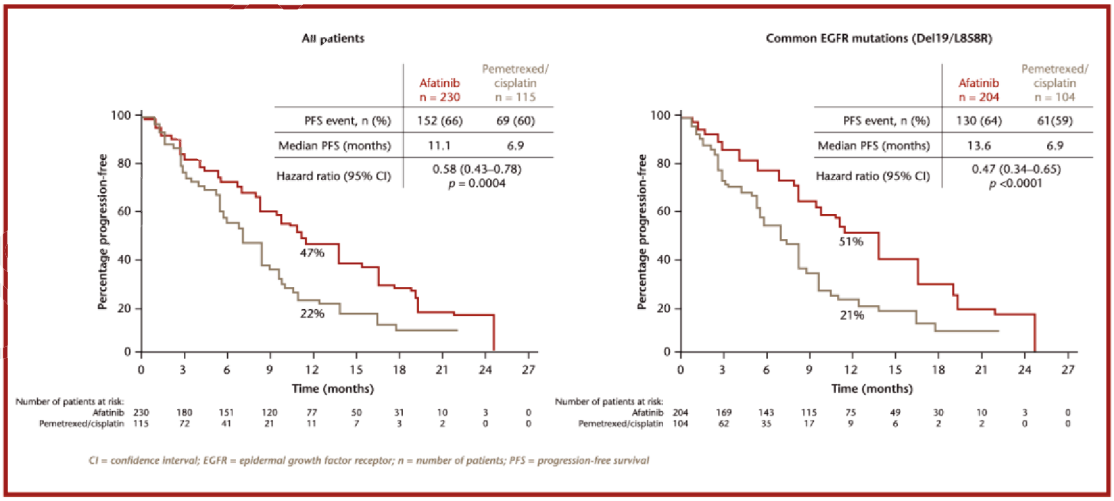


Figure 1. Progression-free survival in LUX-Lung 3.

Afatinib is a second generation, irreversible, ErbB family blocker (ErbB1/EGFR, ErbB2/HER2, and ErbB4/HER4). Afatinib 40 mg po daily as a single agent has been studied in several trials of *EGFR* mutant NSCLC, with improved efficacy compared to chemotherapy. *(10,11,12)* In the LUX-Lung 3 trial, afatinib improved the response rate from 23% to 56% and prolonged PFS from 6.9 to 11.1 months compared to chemotherapy in treatment-naïve patients with *EGFR* mutation positive NSCLC (Figure 1). *(13)* Afatinib has also been shown to improve quality of life

compared to chemotherapy. *(14)* When data from LUX-Lung 3 and LUX-Lung 6 are combined, there is an overall survival (OS) benefit seen with afatinib compared to chemotherapy, with median survival of 27.3 months compared to 24.3 months (p=0.0374. *(15)* This difference is particularly impressive in patients with an exon 19 deletion EGFR mutation, in which median OS is 31.7 months with afatinib compared to 20.7 months with chemotherapy (p=0.0001). *(16)* Although no data currently exists directly comparing afatinib to gefitinib or erlotinib, the activity of this 2nd generation EGFR TKI is likely to be equal to or better than either of the 1st generation TKIs in this setting.

Afatinib Plus Cetuximab in the Treatment of EGFR TKI-resistant NSCLC

Preclinical work in mouse models of *EGFR* mutant lung cancer harboring the *EGFR* T790M mutation has shown that the combination of afatinib and cetuximab results in tumor regression, while neither drug alone was effective. *(17)* These observations led to a Phase Ib/II clinical trial of this drug combination in which patients with *EGFR* mutant lung cancer that was resistant to erlotinib or gefitinib received afatinib 40 mg po daily along with cetuximab at escalating doses starting at 250 mg/m^2 and increasing up to a predefined maximum dose of 500 mg/m^2. *(18)* The dose escalation portion of this trial demonstrated no dose limiting toxicities; therefore the recommended Phase II dose of cetuximab was 500 mg/m^2 IV q 2 weeks when given in combination with afatinib 40 mg po daily. Results of the first 96 evaluable patients treated in the expansion cohort showed an objective response rate of 30%, with 75% of patients showing partial response or stable disease (Figure 2). *(19)* The median PFS was 4.7 months. Importantly,

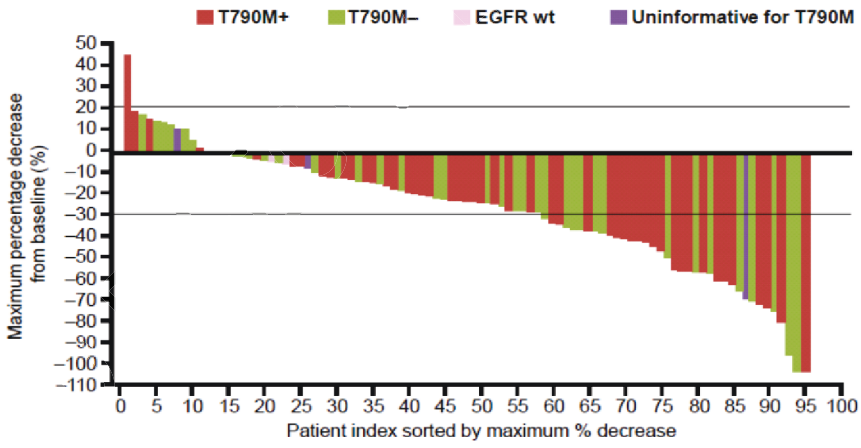


Figure 2

responses occurred in patients with confirmed T790M mutation in their cancers as well as in those that did not have a T790M mutation, which was an unexpected finding given the results of the preclinical studies. Although several other treatment strategies have been pursued in this patient population including erlotinib plus cetuximab and afatinib alone, none have shown the benefit that was seen with the combination of afatinib plus cetuximab. *(20,21,22,23)* Given the promising results in the resistant setting, we hypothesize that patients may derive an even greater benefit if the combination is used in the upfront, treatment-naïve setting with the goal of delaying the development of resistance.

In the Phase Ib/II trial of afatinib and cetuximab, adverse events resulted in trial discontinuation in 19% of patients (Table 1). It is unknown whether the toxicity will be similar when this treatment is used in the first-line setting.

Table 1. Toxicity in the Phase Ib/II Trial of Afatinib/Cetuximab

Patients with adverse event (n=100)	Grade 1-2	Grade ≥ 3	All grades
Rash/acne, n	79	18	97
Diarrhea, n	64	7	71
Fatigue, n	52	9	61
Nausea, n	50	3	53
Xerosis, n	49	3	52
Stomatitis, n	50	1	51
Nail effect, n	48	0	48

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT

	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
RACIAL CATEGORY	**Females**	**Males**	**Females**	**Males**	**TOTAL**
American Indian or Alaskan Native	0	0	0	0	0
Asian	2	3	0	0	5
Black or African American	7	11	0	0	18
Native Hawaiin or other Pacific Islander	1	1	0	0	2
White	87	110	0	1	198
TOTAL	97	125	0	1	223

INTERNATIONAL PLANNED ENROLLMENT REPORT

	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
RACIAL CATEGORY	**Females**	**Males**	**Females**	**Males**	**TOTAL**
American Indian or Alaskan Native	0	0	0	0	0
Asian	0	0	0	0	0
Black or African American	0	0	0	0	0
Native Hawaiin or other Pacific Islander	0	0	0	0	0
White	0	0	0	0	0
TOTAL	0	0	0	0	0

3.0 DRUG INFORMATION

Investigator's Brochures

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, afatinib and cetuximab are considered investigational and are being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Afatinib (afatinib dimaleate, Gilotrif™, BIBW 2992) (NSC # 750691)

a. PHARMACOLOGY

Mechanism of Action

Afatinib binds covalently to the kinase domains of epidermal growth factor receptor (EGFR; ErbB1), human epidermal growth factor receptor 2 (HER2; ErbB2), and human epidermal growth factor receptor 4 (HER4; ErbB4) resulting in irreversible inhibition of tyrosine kinase autophosphorylation that is causing downregulation of ErbB signaling.

In vitro, afatinib inhibits the autophosphorylation and proliferation of cell lines expressing wild-type EGFR or those expressing selected EGFR exon 19 deletion mutations or exon 21 L858R mutations including some with a secondary T790M mutation at concentrations achieved, at least transiently, in patients. In addition, afatinib inhibits *in vitro* proliferation of cell lines overexpressing HER2.
Treatment with afatinib results in inhibition of tumor growth in nude mice implanted with tumors either overexpressing wild type EGFR or HER2 or in an EGFR L858R/T790M double mutant model.

b. PHARMACOKINETICS

1. Absorption: After oral administration of afatinib tablets, the time to peak plasma concentration (Tmax) was 2 to 5 hours. The maximum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC 0-∞) values increased slightly more than dose proportional in the range of 20 to 50 mg. Oral administration of 20mg tablets resulted in a geometric mean relative bioavailability of 92% compared to an oral solution.

2. Distribution: In vitro, afatinib is approximately 95% bound to human plasma proteins.

3. Metabolism: Enzymatic metabolism of afatinib is minimal. Covalent adducts to proteins are the major circulating metabolites of afatinib.

4. Elimination: Afatinib is eliminated mainly by biliary/fecal excretion. Following oral administration of radiolabeled afatinib to humans, excretion of afatinib was primarily via the feces (85%). Four-percent of the dose was recovered primarily unchanged in the urine. The parent compound accounted for 88% of the recovered dose. After repeated

dosing in cancer patients, the elimination half-life of afatinib is 37 hours. Steady state is reached within eight days of repeated dosing with an accumulation of 2.8-fold for AUC and 2.1-fold for Cmax.

Afatinib was not studied in patients with severely impaired renal or liver function. Patient with moderate (creatinine clearance of 30-59mL/min) to severe (creatinine clearance < 30mL/min) renal dysfunction should be closely monitored. Patient with severe hepatic impairment (Child Pugh C) should be closely monitored.

c. ADVERSE EFFECTS

1. Human data:

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2596 patients.* Below is the CAEPR for Afatinib.

Version 2.3, June 15, 2020[1]

Adverse Events with Possible Relationship to Afatinib (CTCAE 5.0 Term) [n= 2596]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
EYE DISORDERS		
	Eye disorders - Other (ocular event)[2]	
GASTROINTESTINAL DISORDERS		
	Cheilitis	
	Constipation	
Diarrhea		
	Dyspepsia	
		Gastrointestinal perforation[3]
Mucositis oral[4]		
Nausea		
		Pancreatitis
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	
HEPATOBILIARY DISORDERS		
		Hepatic failure
INFECTIONS AND INFESTATIONS		
Infections[5]		
INVESTIGATIONS		
	Alanine aminotransfer	

Adverse Events with Possible Relationship to Afatinib (CTCAE 5.0 Term) [n= 2596]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	ase increased	
	Aspartate aminotransferase increased	
	Creatinine increased[6]	
		Ejection fraction decreased
	Weight loss	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hypokalemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Muscle cramp	
NERVOUS SYSTEM DISORDERS		
	Dysgeusia	
RENAL AND URINARY DISORDERS		
	Renal and urinary disorders - Other (renal impairment)[6]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Epistaxis	
	Nasal congestion	
		Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[7]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus	
	Rash acneiform	
	Skin and subcutaneous tissue disorders - Other (nail effect)[8]	

Adverse Events with Possible Relationship to Afatinib (CTCAE 5.0 Term) [n= 2596]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Skin and subcutaneous tissue disorders - Other (rash)[9]		
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis

1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

2 Ocular disorders may include conjunctivitis, conjunctival irritation, conjunctival hyperemia, corneal abrasions, corneal erosion, dry eye, keratitis, ulcerative keratitis, keratopathy, and xerophthalmia.

3 Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

4 Mucositis oral (stomatitis) may include stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, and mucosal ulceration.

5 Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

6 Renal impairment may include acute kidney injury (acute renal failure), acute pre-renal failure, renal impairment, creatinine increased, blood urea increased, glomerular filtration rate increased, and glomerular filtration rate abnormal.

7 Interstial lung disease may include acute interstitial pneumonitis, pneumonitis, acute respiratory distress syndrome, pulmonary infiltrates, and pulmonary fibrosis.

8 Nail effect includes paronychia and nail disorder (e.g., nail ridging, nail loss, and nail discoloration).

9 Rash may include rash, rash pustular, folliculitis, skin fissures, skin exfoliation, dermatitis, erythema, skin reaction, skin ulcer, skin toxicity, skin erosion, skin irritation, and skin swelling.

Adverse events reported on afatinib trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that afatinib caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Bone marrow hypocellular
EAR AND LABYRINTH DISORDERS - Vertigo
GASTROINTESTINAL DISORDERS - Abdominal pain; Dry mouth; Dysphagia; Esophageal stenosis; Esophagitis; Gastritis; Gastroesophageal reflux disease; Oral pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Malaise; Non-cardiac chest pain

IMMUNE SYSTEM DISORDERS - Allergic reaction
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; GGT increased; INR increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Lethargy; Seizure
PSYCHIATRIC DISORDERS - Confusion; Insomnia
RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Proteinuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Reproductive system and breast disorders - Other (female genital tract fistula)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Oropharyngeal pain; Pleural effusion; Productive cough; Respiratory, thoracic and mediastinal disorders - Other (nasal dryness); Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal inflammation)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia
VASCULAR DISORDERS - Hypotension; Vasculitis

Note: Afatinib in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Pregnancy Category D. There are no adequate and well-controlled studies of afatinib use in pregnant women. Animal studies showed that afatinib was embryotoxic and its administration to pregnant rabbits resulted in post implantation loss. In animals showing maternal toxicity, afatinib administration led to abortion at late gestational stages. The effect on rabbit fetuses included reduced fetal weights and increase in the incidences of runts, and visceral and dermal variations. In an embryofetal development study in rats, there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight. Base on its mechanism of action, afatinib is expected to cause fetal harm when administered during pregnancy. Women should be cautioned against becoming pregnant while receiving afatinib.

   It is not known whether afatinib is excreted into human milk. Afatinib was found in the milk of lactating rats at concentrations 80-150 times higher than those present in plasma from 1 to 6 hours after administration.

3. Drug Interactions: Afatinib is an inhibitor and a substrate of the transporter P-glycoprotein (P-gp). Co-administration of P-gp inhibitors with afatinib can increase exposure to afatinib. Co-administration with P-gp inducers can decrease exposure to afatinib.

Based on in vitro data, afatinib is a substrate and an inhibitor of the transporter Breast Cancer Resistance Protein (BCRP).

In vitro, afatinib is not an inhibitor or an inducer of cytochrome P450 (CYP450) enzymes and therefore, it is unlikely to affect the metabolism of drugs that are substrates of CYP450 enzymes. CYTP450 enzymes play a negligible role in the metabolism of afatinib, thus drug interactions with afatinib due to inhibition or induction of CYP450 enzyme is unlikely.

Due to potential drug interactions with the transporter P-gp inhibitors and inducers, the complete patient medication list should be screened prior to initiation of and during treatment with afatinib. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

1. Afatinib is supplied free of charge by Boehringer Ingelheim and distributed by Biologics.

2. Formulation and dose form available:

Afatinib tablets are available as 20mg, 30mg and 40mg tablets in bottles containing 30 tablets. The description of the tablets is: 40 mg: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T40” on one side and the Boehringer Ingelheim company symbol on the other side. 30 mg: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T30” on one side and the Boehringer Ingelheim company symbol on the other side. 20 mg: white to slightly yellowish film-coated, round, biconvex, bevel-edged tablets debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.

f. STORAGE, PREPARATION & STABILITY

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Dispense medication in the original container to protect from exposure to high humidity and light.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: Drug orders must be submitted by faxing the Drug Order Form – SWOG **S1403** to Biologics at the number listed on the order form. This form can be found on the SWOG website (http://swog.org).

2. Drug Handling and Accountability: Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Oral Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI Oral DARF.

3. Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

4. Questions about drug orders, transfers, returns, or accountability should be addressed to protocols@swog.org.

3.2 Cetuximab (IMC-C225, Erbitux®) (NSC-714692)

a. PHARMACOLOGY

Mechanism of Action: Cetuximab, a chimerized antibody of the IgG_1 subclass, was originally derived from a mouse myeloma cell line. Cetuximab was genetically engineered by cloning the heavy and light chains of cetuximab and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization resulted in an antibody with binding affinity to epidermal growth factor receptors (EGFR) greater than the natural ligand epidermal growth factor (EGF). Cetuximab blocks binding of EGF and transforming growth factor alpha (TGFα) to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand.

b. PHARMACOKINETICS

1. Absorption: When cetuximab was administered as monotherapy or in combination with chemotherapy or radiation therapy it exhibited nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while the clearance decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2. The clearance seemed to plateau at doses greater than 200 mg/m^2.

2. Distribution: The volume of distribution of cetuximab is independent of the dose and is approximately the plasma volume (2 to 3 L/m^2). When administered at the recommended dose regimen of 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly dose, the concentration of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations in the range of 168 to 235 and 41 to 85 mcg/mL, respectively.

3. Metabolism: Cetuximab is eliminated via the EGFR binding/internalization on hepatocytes and skin in a saturable manner.

4. Elimination: At the recommended dose regimen, the mean half-life of cetuximab was approximately 112 hours (range 63–230 hours).

c. ADVERSE EFFECTS

1. Possible Side Effects of Cetuximab

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in >20% to 100% of subjects treated with cetuximab include: nail changes, radiation recall, rash, itching, dry skin, acne, dehydration, weight loss, anorexia, mucositis, constipation,

diarrhea, vomiting, nausea, insomnia, headache, fatigue, pain, fever, infection, cough, and dyspnea.

Adverse effects reported in 4% to 20% of subjects include: allergic reaction/hypersensitivity which may cause rash, hypotension, wheezing, shortness of breath, and swelling of the face or throat, confusion, depression, anxiety, syncope, sepsis, and pulmonary embolism.

Adverse effects that are rare and serious that occurred in 3% or less of subjects include: interstitial lung disease, renal failure, and cardiopulmonary arrest and/or sudden death.

Note: Cetuximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Additional information on common, serious, or severe reactions includes:

Infusion Reactions: In clinical trials, severe, potentially fatal infusion reactions were reported. These events included the rapid onset of airway obstruction (bronchospasm, stridor, and hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Approximately 90% of severe infusion reactions occurred with the first infusion despite 116 premedication with antihistamines.

Dermatologic Toxicity: In clinical studies of cetuximab, dermatologic toxicities, including acneiform rash, skin drying and fissuring, and inflammatory and infectious sequelae (e.g. blepharitis, conjunctivitis, keratitis, cheilitis, cellulitis, cyst), and hypertrichosis were reported. In patients with advanced colorectal cancer, acneiform rash was reported in 88% (560/633) of all treated patients, and was severe (Grade 3 or 4) in 12% (79/633) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Non-suppurative acneiform rash described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving cetuximab plus irinotecan and in 90% (10% Grade 3) of patients receiving cetuximab monotherapy. Acneiform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (e.g. blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneiform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

A related nail disorder, occurring in 14% of patients (0.3% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Hypomagnesaemia: In patients treated with cetuximab during clinical trials, hypomagnesemia occurred in 55% of 365 patients with colorectal cancer and head and neck cancer, and was severe (NCI CTC Grades 3 and 4) in 6–17%. The addition of cetuximab to cisplatin and 5-fluoruracil resulted in an increased incidence of hypomagnesemia (14% vs. 6%) and of Grade 3–4 hypomagnesemia (7% vs. 2%) compared to cisplatin and 5-fluorouracil alone. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of cetuximab.

Cetuximab in combination with radiation and cisplatin: The addition of cetuximab to radiation therapy and cisplatin in a study of patients with locally advanced squamous cell cancer of the head and neck (SCCHN) resulted in an increase in the incidence of Grade 3–4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone. Adverse reactions with fatal outcome were reported in 20 patients (4.4%) in the cetuximab combination arm and 14 patients (3%) in the control arm. Nine patients in the Erbitux arm (2%) experienced myocardial ischemia compared to 4 patients (0.9%) in the control arm.

2. Pregnancy and Lactation: Pregnancy Category C. There are no adequate and well-controlled studies of cetuximab in pregnant women. Based on animal studies, EGFR has been involved in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Human IgG is known to cross the placental barrier; therefore, if administered to a pregnancy woman, cetuximab may be transmitted from the mother to the developing fetus and has the potential to cause fetal harm.

   It is not known whether cetuximab is secreted in human milk. IgG antibodies, such as cetuximab, can be excreted in human milk and has the potential to cause serious adverse reactions in the nursing infant. Base on the mean half-life of cetuximab, nursing should not resume for at least 60 days following the last dose of cetuximab.

3. Drug Interactions: There are no reports of drug interactions with cetuximab.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

The product is formulated to 2 mg protein/mL with phosphate buffered saline, pH 7.2 ± 0.2 and aseptically filled into sterile glass vials, 100 mg per 50 cc vial, and stored as a liquid at 2 to 8 °C. Each vial contains the following active and inactive ingredients per 1.0 ml: 2 mg of cetuximab, 145 nmol/L sodium chloride, and 10 mmol/L sodium phosphate.

Cetuximab is commercially available, but will be supplied for this study by Eli Lilly and Company and distributed by Biologics. Quantities must be ordered in multiples of 20 (keeping in mind that 7 - 9 vials will be needed for an initial dose and 4 - 6 for a maintenance dose, depending on patient's BSA). A suggested

initial shipment is 20 vials. Institutions should reorder when supply is low based on site needs. Drug orders must be submitted by faxing the Drug Order Request Form – SWOG **S1403** to Biologics as noted on the order form. This form can be found on the SWOG website (http://swog.org).

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

4.0 STAGING CRITERIA

Stage IV Any T Any N M1a or M1b

Distant Metastasis (M)

M1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion

M1b Distant metastasis (in extrathoracic organs)

* Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via MediData Rave ® (see Section 14.0). Any potential eligibility issues should be addressed to the Statistics and Data Operations Center in Seattle at 206/652-2267 prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have histologically or cytologically confirmed Stage IV (AJCC 7th Edition) or recurrent non-small cell lung cancer (NSCLC).

b. Patients must have documented presence of an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation. T790M mutation or other molecular abnormality will be allowed as long as it accompanies one of the mutations listed above. EGFR testing must have been performed using a FDA-approved test or in a CLIA-certified laboratory.

c. Patients must have tissue available and must agree to submission of tissue and blood as outlined in Section 15.0. One to two paraffin-embedded tissue blocks or 15-20 unstained slides are requested (a minimum of 12 slides is required).

Cytology (i.e. fine-needle aspirations, pleural effusion specimens) is acceptable if a cell block or sufficient unstained slides are available. Tumor material must be reviewed by a local pathologist who must confirm that at least 100 viable tumor cells are present in the sample and sign the **S1403** Pathology Review Form prior to registration. Patients must also be willing to submit blood samples for correlative research at baseline, during treatment and at progression.

d. Patients enrolled at sites participating in the Repeat Biopsy Study must agree to submission of tissue obtained by a repeat biopsy performed at the time of disease progression.

e. Patients must not have received any prior systemic anticancer therapy for advanced or metastatic disease including chemotherapy or EGFR tyrosine kinase inhibitor therapy (including gefitinib, erlotinib, afatinib, or any experimental EGFR TKI agents). Prior chemotherapy for non-metastatic disease (i.e. adjuvant therapy or concurrent chemo-radiotherapy) is allowed as long as >12 months has passed since completion of therapy. Adjuvant EGFR-directed therapy is not allowed. Local therapy (i.e. palliative radiotherapy) is allowed as long as a period of 7 days has passed since the last dose was received and the patient has recovered from any associated toxicity at the time of registration.

f. Patients may have measurable or non-measurable disease (see Section 10.1) documented by CT or MRI within 42 days prior to registration. The CT from a combined PET/CT may be used only if it is of diagnostic quality as defined in Section 10.1a. Laboratory parameters are not acceptable as the only evidence of disease. In order to qualify as measurable per Section 10.1a, measurable disease must be outside previous radiation field. All disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

g. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to registration. Patient must not have symptomatic brain metastases or evidence of leptomeningeal carcinomatosis. Patients with asymptomatic brain metastases are eligible if off of steroids for at least 7 days prior to registration without development of symptoms.

5.2 Clinical/Laboratory Criteria

a. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500/mcL; platelets ≥ 75,000/mcL; and hemoglobin ≥ 9 g/dL. These results must be obtained within 28 days prior to registration.

b. Patients must have adequate liver function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN), and AST and ALT ≤ 2.5 x IULN (or ≤ 5 x IULN for patients with known liver metastases). These results must be obtained within 28 days prior to registration.

c. Patient must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ 1.5 x IULN OR measured or calculated creatinine clearance ≥ 60 mL/min. This result must have been obtained within 28 days prior to registration.

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

d. Patients must not have significant gastrointestinal disorders with diarrhea as a major symptom (e.g. Crohn's disease, malabsorption, etc).

e. Patients must be able to swallow medication by oral route.

f. Patients must not have a history of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3 (see Section 18.5), unstable angina or poorly controlled arrhythmia or myocardial infarction New York Heart Association Criteria within 6 months prior to registration. If clinically indicated, echocardiogram or MUGA must be performed and cardiac ejection fraction must be ≥ 50%

g. Patients must not have had major surgery within 28 days prior to registration or be scheduled for surgery during the projected course of protocol treatment. Tumor biopsy is allowed.

h. Patients must not have a known history of active hepatitis B infection (defined as presence of Hep B sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV seropositive.

i. Patients must not have any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the study drug.

j. Patients must not be planning to receive any other investigational agents during the course of protocol treatment.

k. Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to afatinib and/or cetuximab.

l. Prestudy history and physical must be obtained with 28 days prior to registration.

m. Patients must have Zubrod Performance Status of 0 - 2 (see Section 10.4).

n. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.

o. Patients must not be pregnant or nursing because of the risk of fetal harm including fetal death. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5.3 Regulatory Criteria

a. Pat*ients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.*

b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be randomized between Arm 1 (afatinib and cetuximab) and Arm 2 (afatinib) using a dynamic balancing algorithm. *(24)*

Stratification is based on performance status (0-1 vs 2) and EGFR mutation type (exon 19 deletion versus L858R mutation).

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Goldberg at 203-785-7564 or sarah.goldberg@yale.edu or Dr. Lilenbaum at 203-200-2094 or rogerio.lilenbaum@yale.edu. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "About" then "Policies and Procedures" and choose Policy 38).

7.1 Pre-Medication

All patients who will receive cetuximab will be premedicated with:

Agent	Dose	Route	Duration
Diphenhydramine	50mg	IV	prior to the first dose of cetuximab hydrochloride

Diphenhydramine must be given prior to the first dose of cetuximab in an effort to prevent a hypersensitivity reaction. Premedication is recommended prior to subsequent doses, but at the treating physician's discretion, the dose of diphenhydramine may be reduced.

Consideration may be given to administering magnesium sulfate 2g IV prior to cetuximab infusion in an effort to prevent hypomagnesemia.

7.2 Treatment

Patients will be randomized to Arm 1 or Arm 2.

a. Arm 1

Agent	Dose	Route	Day	Schedule*
Afatinib	40 mg	PO	1-28	Daily**
Cetuximab	500 mg/m^2	2 hour IV infusion	1 and 15	q 28 days

* Note: One cycle = 28 days.
** Afatinib must not be taken with food. Take on an empty stomach at least 1 hour before or 2 hours after a meal. Do not take a missed dose within 12 hours of the next dose.

Treatment will continue as above until one of the criteria in Section 7.6 is met.

b. Arm 2

Agent	Dose	Route	Day	Schedule*
Afatinib	40 mg	PO	1-28	Daily**

* Note: One cycle = 28 days.
** Afatinib must not be taken with food. Take on an empty stomach at least 1 hour before or 2 hours after a meal. Do not take a missed dose within 12 hours of the next dose.

Treatment will continue as above until one of the criteria in Section 7.6 is met.

7.3 Drug Compliance Documentation

The study medication will be given in accordance with the protocol and the instructions of a site investigator. The appropriate number of afatinib tablets for 4 weeks of treatment will be provided to patients to be self-administered at home. Patients will be asked to bring the remaining trial medication at the end of each visit to the investigator site for a compliance check. The remaining film-coated tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. At the end of each 4 week period, any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of study medication must be dispensed.

The investigator can withdraw a patient from the study in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render study results for this patient unacceptable. Patients who do not attend a minimum of *75%* of scheduled study visits, unless due to exceptional circumstances, should be evaluated for compliance.

Drug compliance will be recorded by patients in the Intake Calendar (see Section 18.2). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.4 Concomitant medications or therapy

a. Concomitant medication

Afatinib is a substrate of P-gp and the use of Ps-gp inhibitors or inducers should be avoided. Common medications that should be avoided are reported below.

Inhibitors	Inducers
Amiodarone	Carbamazepine
Azithromycin	Phenytoin
Captopril	Rifampicin
Carvedilol	St John's Wort
Clarithromycin	Phenobarbital Salt
Conivaptan	Tipranavir
Cyclosporine	Ritonavir
Diltiazem	
Dronedarone	
Erythromycin	
Felodipine	
Itraconazole	
Ketoconazole	
Lopinavir	
Nelfinavir	
Ritonavir	
Quinidine	
Ranolazine	
Saquinavir	
Tacrolimus	
Ticagrelor	
Verapamil	

Prior to initiation of therapy, patients should be informed that they may experience diarrhea, and consideration may be given to providing patients prophylactic anti-diarrheal medication. One example of a prophylactic regimen is the following:

Loperamide 4 mg with the first dose of afatinib, followed by 2 mg every 4 hours for the first 3 days. After the first 3 days, take loperamide 2 mg every 6-8 hours until the end of the first cycle of therapy whether the patient is experiencing diarrhea or not. Beyond the first cycle it may be continued at the discretion of the treating physician. Loperamide should be held if constipation develops.

b. Radiotherapy

After study enrollment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area cannot be used for tumor response assessment. During palliative radiotherapy, protocol treatment should be held and may be resumed once the

patient has recovered from any radiation associated toxicity. Continuous interruption of >28 days due to palliative radiotherapy will not be allowed; in such a circumstance the patient must be removed from protocol treatment.

c. Surgery

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib and cetuximab around one week prior to the surgery, and to restart treatment after complete wound healing. If afatinib or cetuximab is interrupted for more than 28 days, the patient must be removed from protocol treatment.

d. Tumor biopsy

At select institutions, patients will be required to undergo a repeat tumor biopsy at the time of disease progression following an initial response. Repeat biopsies will be obtained **only** from patients who have disease progression after one of the following treatment responses:

- Objective response (complete or partial response), or
- Stable disease ≥ 6 months.

The biopsy site should be chosen based on safety and the presence of tumor growth at that site. Afatinib and cetuximab do not need to be held around the time of the biopsy. See Section 15.5 and 15.6 for more details.

7.5 Emergency Procedures

Cetuximab: Allergic reactions may occur during or following cetuximab administration. As a routine precaution, patients enrolled in this study will be observed closely for any potential adverse events by the medical staff from the start of the cetuximab infusion to one hour after the end of the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. Vital signs (blood pressure, heart rate, respiratory rate and temperature) should be checked prior to the administration, midway through the infusion, at the completion of the infusion and 1 hour post the infusion. Should an allergic or infusion reaction to cetuximab occur, the patient must be treated according to the best available medical practices. The cetuximab infusion rate should never exceed 5 mL/minute. Epinephrine and diphenhydramine for injection should be readily available during the infusion, for emergency treatment of hypersensitivity reactions. See Section 8.3c for additional details.

Afatinib: Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for overdosage with afatinib. Potential adverse events should be treated symptomatically. Common adverse events of treatment with afatinib with specified management recommendations and/or requirements include diarrhea, nausea, rash/acne, and mucositis/stomatitis. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. See Section 8.0 for details.

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude interstitial lung disease (ILD). Study drugs should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug must be permanently discontinued and appropriate treatment instituted as necessary.

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is

confirmed, treatment with afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration

7.6 Criteria for Removal from Protocol Treatment

a. Unequivocal progression of disease or symptomatic deterioration (as defined in Section 10.2e). Patients may continue to receive study treatment after radiographic progression per RECIST 1.1 as long as they continue to experience clinical benefit in the opinion of the treating physician. Patients who continue to receive study treatment after progression will continue with the on study requirements (as indicated by the study calendar "Cycle X" columns), **not** the off study requirements (as indicated by the study calendar column titled "F/U After Prog").

b. Unacceptable toxicity.

c. Women who become pregnant while participating in the study must discontinue study medication immediately. The pregnancy must be reported following procedures detailed in Section 16.1.

d. Treatment delay for any reason > 28 days from planned date of treatment.

e. The patients may withdraw from the study at any time for any reason.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.8 Follow-Up Period

All patients will be followed until death or 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Dose Modification Guidelines

a. Missed doses are to be omitted rather than made up.

b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. Reductions are based on the dose given in the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.

d. If treatment is held > 28 days due to any reason, patient must be removed from protocol treatment.

8.3 Dose Modifications

a. Dose Modifications for Afatinib Plus Cetuximab (Arm 1)

Drug	Level 0	Level -1	Level -2	Level -3	Level -4
Afatinib	40 mg	30 mg	30 mg	30 mg	20 mg
Cetuximab	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue	--

Note: Once a dose reduction is applied, the reduced dose is maintained unless further dose reduction is needed.

For patients with CTCAE grade ≥3 drug related hypomagnesemia, only cetuximab dose should be reduced; there is no need to reduce the afatinib dose.

b. Dose Modifications for Afatinib Alone (Arm 2)

Drug	Level 0	Level -1	Level -2
Afatinib	40 mg	30 mg	20 mg

Note: Once a dose reduction is applied, the reduced dose is maintained unless further dose reduction is needed.

c. Hypersensitivity Reaction

In each case of hypersensitivity reaction, the investigator should institute treatment measures according to the best available medical practice. Based on previous experience with cetuximab hypersensitivity reactions, the following treatment guidelines may be applicable:

Toxicity Grade	Cetuximab modification
1	Decrease cetuximab infusion rate by 50% and monitor closely for any worsening.
2	Stop cetuximab infusion. Administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate after allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity. Monitor closely for any worsening.
3 or 4	Stop cetuximab infusion immediately and disconnect infusion tubing from patient. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc. as medically necessary. Discontinue all further cetuximab treatment.*

* Patients with CTCAE Grade ≥3 allergic reaction/hypersensitivity which can clearly be attributed to cetuximab will result in the permanent discontinuation of that drug only, with continuation of afatinib if deemed by the investigator that patient derived clinical benefit from continuation of afatinib.

d. Hypomagnesemia

Toxicity Grade	Cetuximab modification
1	Magnesium chloride starting at 2 tablets PO three times a day, titrating up to 4 tablets PO three times a day as needed. Treating physician may also consider weekly magnesium monitoring without replacement for Grade I hypomagnesemia in asymptomatic patients without cardiac history or cardiac risks.
2	Weekly intravenous replacement with magnesium sulfate 4 g.
3 or 4	Magnesium sulfate 6 to 10 g IV twice weekly, dependent on the patient. An initial strategy of IV replacement and every-other-day serum magnesium monitoring is helpful to guide the frequency of replacement until a steady state is reached. In a patient with normal renal function, start amiloride 5 mg PO daily and titrate up to 10 mg PO daily. Afatinib may be continued. Cetuximab should be held until recovery to Grade 2 or less. Upon recovery, resume cetuximab at next reduced dose level (afatinib dose does not need to be reduced). If ≥ Grade 3 hypomagnesemia does not resolve to ≤ Grade 2 within 28 days of stopping cetuximab and despite optimal supportive care, discontinue cetuximab.

e. Diarrhea

Close monitoring and proactive management of diarrhea is essential for successful treatment of patients with afatinib with or without cetuximab. Early and appropriate intervention can prevent the development of more severe diarrhea. In most cases, loperamide controls diarrhea caused by afatinib. Loperamide should be available at the start of therapy and kept with the patient at all times; it is therefore advisable that patients be given a prescription at the time of initiating

treatment with afatinib. Patients should be instructed to take two 2 mg loperamide tablets after the first episode of diarrhea, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg). In patients who have persistent diarrhea despite loperamide, a step-wise increase in anti-diarrheal therapy should be employed. Diphenoxylate/atropine (Lomotil) can be added (recommended dose of two 5 mg tablets up to 4 times daily, for a maximum daily dose of 20 mg) as can tincture of opium (recommended dose of 6 mg [or 10 mg/mL] up to 4 times daily, for a maximum daily dose of 24 mg [or 40 mg/mL]).

Toxicity Grade	Modification
1	Two 2 mg loperamide tablets should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg). Add other anti-diarrheal agents as described above if necessary.
2	As with Grade 1, and appropriate rehydration (1.5 L/m^2/day plus equivalent of actual fluid loss) and electrolyte replacement.
2 lasting $\geq$ 2 days	May be treated in manner similar to Grade 2 diarrhea. Treatment must be stopped until recovery to ≤ Grade 1. Upon recovery, treatment should be resumed at next reduced dose level. If despite optimal supportive care and a treatment pause diarrhea does not resolve to Grade ≤ 1 within 28 days of stopping treatment and despite optimal supportive care, discontinue protocol treatment.
3 or 4	May be treated in manner similar to Grade 2 diarrhea. Treatment must be paused until resolution to ≤ Grade 1. Upon recovery, treatment should be resumed at next reduced dose level. If despite optimal supportive care and a treatment pause diarrhea does not resolve to Grade ≤ 1 within 28 days of stopping treatment and despite optimal supportive care, discontinue protocol treatment.

f. Nausea and Vomiting

Toxicity Grade	Modification
Nausea 1 & Vomiting 0	Antiemetic treatment*, if deemed necessary by treating physician.
Nausea 2 & Vomiting 0 or Nausea 0-2 & Vomiting 1-2	Antiemetic treatment*. Hold study treatment if Grade 2 vomiting or Grade 2 nausea persists for 7 or more consecutive days despite optimal supportive care. Resume treatment at next reduced dose level when recovered to ≤ Grade 1.
Vomiting 3 or 4 or Nausea 3 or 4	Antiemetic treatment*. Hold study treatment until recovery to ≤ Grade 1 or baseline. Resume treatment at next reduced dose level when recovered to ≤ Grade 1. If ≥ Grade 3 nausea or vomiting does not resolve to ≤ Grade 1 within 28 days of stopping treatment and despite optimal supportive care, discontinue protocol treatment.

* Antiemetic treatment should follow the recommendations give in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference (R06-0986).

g. Rash, Acne, Paronychia

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and to reduce the rash.

1. General/Prevention

a. Patients should be educated on the importance of taking afatinib on an empty stomach.

b. Hypoallergenic moisturizing creams, ointments and emollients should be used once or twice daily to prevent and alleviate skin dryness. Avoid topical acne medications. Use of gentle soaps (e.g. Dove unscented soap, Cetaphil cleansing lotion) and gentle shampoos.

c. Patients should be cautioned about sun exposure, which can make the rash worse. Hypoallergenic sunscreen with a high SPF (at least SPF30, PABA free, UVA/UVB protection), preferably broad spectrum protection and/or physical blockers containing zinc oxide or titanium dioxide, should be applied to sun-exposed areas every two hours while in the sun (including exposure through windows). Protective clothing for sun protection and wearing a hat and sunglasses should be recommended.

d. To prevent paronychia, patients should keep their hands dry and out of water whenever possible. They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. Trimming cuticles is discouraged as it increases risk for infection. Topical application of petrolatum around the nails is recommended.

e. The use of prophylactic oral antibiotics (e.g. doxycycline 100 mg twice daily or minocycline 100 mg twice daily) has been shown to be effective in preventing or reducing the severity of skin toxicity associated with EGFR inhibitors. The prophylactic use of these agents can be considered for individual patients.

2. Management

Toxicity Grade	Management
1	Mild rash may not need treatment. However, if treatment is considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% lotion applied twice daily can be used.
2	Relief from major symptoms should be achieved by a combination of therapies including: systemic antibiotics (e.g. doxycycline 100 mg twice daily or minocycline 100 mg twice daily), topical treatment (e.g. for extremities and trunk use topical clobetasol 0.05% twice daily for up to two weeks; for face use hydrocortisone valerate 0.2% twice daily for up to two weeks or pimecrolimus 1% cream twice daily; for pustules use clindamycin 1% twice daily), antihistamines (e.g. diphenhydramine, etc), or oral corticosteroids at treating physician's discretion. Systemic and topical treatment should be initiated at the start of Grade 2 rash and continued until improvement or resolution to ≤ Grade 1. If Grade 2 rash persists for ≥ 7 days despite treatment and is poorly tolerated by patient, treatment may be held for up to 28 days. Resume treatment at next reduced dose level when recovered to ≤ Grade 1. If ≥ intolerable Grade 2 rash does not resolve to ≤ Grade 1 within 28 days of stopping treatment and despite optimal supportive care, discontinue protocol treatment.
3 or 4	May be treated in manner similar to Grade 2 rash. Additionally, treatment should be paused until resolution to ≤ Grade 1. Resume treatment at next reduced dose level when recovered to ≤ Grade 1. If ≥ Grade 3 rash does not resolve to ≤ Grade 1 within 28 days of stopping treatment and despite optimal supportive care, discontinue protocol treatment.

3. Management of paronychia is based on anecdotal evidence. Warm soaks and/or topical application for hydrocortisone 2.5% cream is recommended for symptomatic relief. Topical antibiotics (e.g. Burow's solution or aluminum acetate soaks, 4% thymol in alcohol, silver nitrate application) or systemic antibiotics may also be recommended. Patients may try liquid cyanoacrylates (e.g., Band-Aid® Liquid Bandage) to relieve pain and promote healing of fissures.

h. Mucositis, Stomatitis

Treatment is supportive and aimed at symptom control. Recommendations are summarized in the table below. Avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide can be helpful. Dietary maneuvers such as promotion of soft, non-irritating foods like ice-creams, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, nuts and alcohol is also recommended. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed.

Toxicity Grade	Modification
1	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution.
2	Addition of topical analgesic mouth treatments, topical corticosteroids (clobetasol 0.05% gel), antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.
3 or 4	Same management as for Grade 2. Institute additional symptomatic therapy (topical or systemic) as clinically indicated. Additionally, treatment should be paused until resolution to ≤ Grade 1. Resume treatment at next reduced dose level when recovered to ≤ Grade 1. If ≥ Grade 3 mucositis/stomatitis does not resolve to ≤ Grade 1 within 28 days of stopping treatment and despite optimal supportive care, discontinue protocol treatment.

i. Pulmonary

Toxicity Grade	Modification
3 or 4	Hold all protocol treatment. If interstitial lung disease (ILD) is confirmed or strongly suspected, discontinue protocol treatment and treat appropriately. If an alternative diagnosis is made, protocol treatment can be resumed.

j. Hepatic

Toxicity Grade	Modification
SGOT or SGPT Grade 0-1 And Bilirubin Grade 0-2	No change
SGOT or SGPT Grade 2-4 Or Bilirubin Grade 3-4	Hold all protocol treatment until resolution to ≤ Grade 1 or back to baseline values. Resume treatment at one reduced dose level when recovered. If toxicity does not resolve to ≤ Grade 1 or baseline within 28 days of stopping treatment, discontinue protocol treatment.
SGOT or SGPT Grade 2-4 And Concomitant Bilirubin > 2 x IULN	Discontinue protocol treatment.

k. Other toxicity: For any other medically concerning toxicity ≥ Grade 2, consider holding treatment until toxicity resolves to ≤ Grade 1 and reduce dose by one dose level upon resuming treatment. If toxicity does not resolve to ≤ Grade 1 within 28 days of stopping treatment and despite optimal supportive care, discontinue protocol treatment. For any medically concerning event ≥ Grade 2, please contact the Study Chairs as needed.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Goldberg at 203-785-7564 or sarah.goldberg@yale.edu or Dr. Lilenbaum at 203/200-2094 or rogerio.lilenbaum@yale.edu.

8.5 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 STUDY CALENDAR – ARM 1: AFATINIB PLUS CETUXIMAB

										Σ								Ω	%
		Cycle 1				Cycle 2				Cycle 3				Cycle 4				F/U Prior to Prog	F/U After Prog
REQUIRED STUDIES ã	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
	STUDY	1	2	3	4	5	6	7 α	8	9	10	11 α	12	13	14	15 α	16		
PHYSICAL																			
History and Physical Exam β	X	X				X				X				X				X	
Weight and Performance Status	X	X	X	X	X	X		X		X		X		X		X		X	X
Disease Assessment	X									X								X	
Toxicity Notation		X	X	X	X	X		X		X		X		X		X		X	X
Vital Signs ?		X		X		X		X		X		X		X		X			
LABORATORY																			
CBC/Differential/Platelets	X	X	X	X	X	X		X		X		X		X		X		X	X
Serum Sodium, Potassium and Magnesium	X	X	X	X	X	X		X		X		X		X		X		X	X
Serum creatinine/ Calculated creatinine clearance	X	X	X	X	X	X		X		X		X		X		X		X	X
Albumin	X	X	X	X	X	X		X		X		X		X		X		X	X
Total protein	X	X	X	X	X	X		X		X		X		X		X		X	X
Serum bilirubin	X	X	X	X	X	X		X		X		X		X		X		X	X
Alkaline phosphatase	X	X	X	X	X	X		X		X		X		X		X		X	X
AST and ALT	X	X	X	X	X	X		X		X		X		X		X		X	X
INR δ		X	X	X	X	X		X		X		X		X		X		X	X
SPECIMEN SUBMISSION																			
Tissue for banking & correlative studies £	X																		X ¥
Blood, Buffy coat, & Plasma £	X									X									X

Calendar continues on next page. Click here for Footnotes

										∑								Ω	%
		Cycle 1				Cycle 2				Cycle 3				Cycle 4				F/U Prior to Prog	F/U After Prog
REQUIRED STUDIES ã	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
	STUDY	1	2	3	4	5	6	7 α	8	9	10	11 α	12	13	14	15 α	16		
X-RAYS AND SCANS																			
PET scan ¿	X																		
CT of chest and abdomen	X									X								X	
Brain CT or MRI	X									X◇								X◇	
ECHO or MUGA §	X																		
ECG §	X																		
TREATMENT																			
Afatinib		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Cetuximab ¶		X		X		X		X		X		X		X		X			

Footnotes for Calendar 9.1:

∑ Protocol treatment and physical, laboratory, and scan parameters will continue at the intervals indicated in the Cycle 3 and 4 columns until progression of disease or until patient has met any of the guidelines in Section 7.6.

£ Required specimen submission for patients. See Section 15.2-15.4 for additional information.

δ Only if patient is on warfarin.

α This visit is only required for patients on cetuximab.

β Physical exam to include cardiopulmonary examination, examination of abdomen and regional lymph nodes, and assessment of mental and neurological status.

Ω After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 8 weeks until progression.

% After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 6 months for three years from the time of registration.

¥ If institution is participating in repeat biopsy substudy. See Section 15.5 and 15.6.

◇ Only if patient has brain metastases at baseline.

§ Only if clinically indicated.

¶ Diphenhydramine must be given prior to first dose of cetuximab and is recommended prior to subsequent doses (see Section 7.1).

? Vital signs should be checked prior to each cetuximab administration, midway through the infusion, at the completion of the infusion, and one hour post the infusion.

ã See “Best Practices for SWOG Studies” at the following URL for acceptable time windows for procedures and assessments: https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

¿ PET scans are recommended as a complement to other scans (see Section 10.2d). They are not required.

9.2 STUDY CALENDAR – ARM 2: AFATINIB ALONE

										Σ								Ω	%
		Cycle 1				Cycle 2				Cycle 3				Cycle 4				F/U Prior to Prog	F/U After Prog
REQUIRED STUDIES ã	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
PHYSICAL																			
History and Physical Exam β	X	X				X				X				X				X	
Weight and Performance Status	X	X	X	X	X	X				X				X				X	X
Disease Assessment	X									X								X	
Toxicity Notation		X	X	X	X	X				X				X				X	X
LABORATORY																			
CBC/Differential/Platelets	X	X	X	X	X	X				X				X				X	X
Serum Sodium and Potassium	X	X	X	X	X	X				X				X				X	X
Serum Creatinine/ Calculated Creatinine Clearance	X	X	X	X	X	X				X				X				X	X
Albumin	X	X	X	X	X	X				X				X				X	X
Total Protein	X	X	X	X	X	X				X				X				X	X
Serum Bilirubin	X	X	X	X	X	X				X				X				X	X
Alkaline Phosphatase	X	X	X	X	X	X				X				X				X	X
AST and ALT	X	X	X	X	X	X				X				X				X	X
INR δ		X	X	X	X	X				X				X				X	X
SPECIMEN SUBMISSION																			
Tissue for banking & correlative studies £	X																		X ¥
Blood, Buffy coat, & Plasma £	X									X									X

Calendar continues on next page. Click here for Footnotes.

										∑								Ω	%
		Cycle 1				Cycle 2				Cycle 3				Cycle 4				F/U Prior to Prog	F/U After Prog
REQUIRED STUDIES ã	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
X-RAYS AND SCANS																			
PET scan ¿	X																		
CT of chest and abdomen	X									X								X	
Brain CT or MRI	X									X◇								X◇	
ECHO or MUGA §	X																		
ECG §	X																		
TREATMENT																			
Afatinib		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Footnotes for Calendar 9.2:

∑ Protocol treatment and physical, laboratory, and scan parameters will continue at the intervals indicated in the Cycle 3 and 4 columns until progression of disease or until patient has met any of the guidelines in Section 7.6.
£ Required specimen submission for patients. See Section 15.2-15.4 for additional information.
δ Only if patient is on warfarin.
β Physical exam to include cardiopulmonary examination, examination of abdomen and regional lymph nodes, and assessment of mental and neurological status.
Ω After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 8 weeks until progression.
% After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 6 months for three years from the time of registration.
¥ If institution is participating in repeat biopsy substudy. See Section 15.5-15.6.
◇ Only if patient has brain metastases at baseline.
§ Only if clinically indicated.
ã See “Best Practices for SWOG Studies” at the following URL for acceptable time windows for procedures and assessments: https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.
¿ PET scans are recommended as a complement to other scans (see Section 10.2d). They are not required.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease:** Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. A malignant lymph node is to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default

measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Time to Treatment Failure

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), early discontinuation of treatment, or death due to any cause. Patients last known not to have failed treatment are censored at the date of last contact.

10.6 Time to Treatment Discontinuation

From date of registration to date of discontinuation of treatment or death due to any cause. Patients last known not to have discontinued treatment are censored at the date of last contact.

10.7 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.8 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size with Power Justification

The primary objective of the Phase III study is to compare overall survival (OS) in *EGFR* mutation positive, previously untreated, advanced NSCLC patients randomized to afatinib plus cetuximab versus afatinib alone. The primary objective of the Phase II interim analysis is to evaluate if there is sufficient evidence to continue to the Phase III component by comparing progression-free survival (PFS) between patients randomized to afatinib alone versus afatinib in combination with cetuximab in this study.

Randomization will be stratified by performance status (0-1 versus 2) and EGFR mutation type (exon 19 deletion versus L858R mutation). It is assumed that among patients with the exon 19 deletion, the median OS with afatinib alone will be 32 months based on the LUX-Lung 3 and 6 studies. It is also assumed that 56% of patients will have the exon 19 deletion. Further, it is assumed that among patients with the L858R mutation, the median OS with afatinib alone will be 21 months also based on the LUX-Lung studies. The median PFS for patients is assumed to be 13.7 months for patients with the exon 19 deletion and 10.8 months among patients with the L858R mutation among patients randomized to afatinib alone based on the LUX-Lung 3 study.

The addition of cetuximab will be judged to be superior if the true increase in median OS is 45% (hazard ratio = 0.69). A design with 90% power (not adjusting for Phase II analysis) and 0.025 1-sided type I error would require 304 deaths. Assuming exponential survival and uniform accrual, with 48 months of accrual and 14 months of follow-up, this design results in a sample size of 576 eligible *EGFR*-mutant NSCLC patients to detect a 45% improvement in median PFS using a 1-sided 0.025 level stratified log-rank test. Under these design parameters, an observed 25% or greater improvement in median OS (equivalent to an increase in median OS of 8 and 5.5 months for exon 19 and L858R patients will be considered evidence of benefit with the addition of cetuximab to afatinib. Assuming a 5% ineligibility rate, the total target accrual is 605.

11.2 Analysis Plan Including Plans for Formal Interim Analysis

a. Phase II Interim Analysis

The Phase II interim analysis will evaluate early stopping for futility alone based on PFS. A design with 90% power to detect a 90% increase in median PFS (from

13.7 to 26 months among exon 19 deletion patients and from 10.8 to 20.5 among L858R mutation patients) and 10% type I error would require 64 progression events. The Phase II interim analysis will take place upon the observation of 64 PFS events, approximately 17 months after study activation when it is expected that 212 patients have been accrued. Conditions for recommending stopping the study early for lack of efficacy will be if the alternative hypothesis is rejected at the 10% level using a 1-sided modified log-rank test. Under these design parameters, an observed 38% or greater improvement in median PFS (equivalent to an increase in median PFS of 5.2 and 4.1 months respectively for exon 19 and L858R strata) will be considered evidence of benefit with the addition of cetuximab to afatinib. In addition to the PFS assessment, toxicity rates will be evaluated and compared between the two arms at this analysis. An additional objective of the Phase II interim analysis will be to evaluate the safety of cetuximab in combination with afatinib. Toxicities of specific focus will be grade ≥ 3 rash and diarrhea.

b. Phase III Interim Analyses

A second interim analysis evaluating early signs of efficacy or futility will take place when 152 (50% of expected) deaths have been observed, approximately 40 months after study activation, when approximately 80% of patients have been accrued to the study. This analysis will evaluate stopping early for efficacy testing the null hypothesis using a 1-sided 0.0025 level log-rank test and stopping early for futility testing the alternative hypothesis at the 0.01 level using a modification of the test allowing for relative risks not equal to one (the approximate HR threshold for futility is 1.00). Should the study not cross any boundaries, the study will continue accrual to the second and final interim analysis.

A final interim analysis will take place when 75% of the expected deaths (228) have been observed, which is expected to take place around completion of accrual at 50 months after activation. The same rules for early stopping for either futility or efficacy will be implemented at this analysis. Should no boundaries be crossed, the recommendation will be to continue to full follow-up.

The final analysis will take place upon the observation of 304 deaths (expected around 14 months after completion of accrual) or at maximum of 2 years after the last patient was accrued, whichever comes first. This analysis will be performed using a 1-sided log-rank test, with significance level of 0.024 to account for the interim analyses.

					Approximate HR Boundary	
Analysis	Information	Events	Anticipated accrual n (%)	Study time	Futility	Efficacy
Phase II interim	14% PFS events*	64 PFS	212 (37%)	17 months	1.38	N/A
Phase III interim #1	50% OS events	152 OS	461 (80%)	40 months	1.006	1.56
Phase III interim #2	75% OS events	228 OS	576 (100%)	50 months	1.07	1.44
Final Analysis	100% OS events	304 OS	576 (100%)	62 months	1.25	1.25

* The expected number of PFS events by the end of the Phase III is 446.

c. **REVISED STATISTICAL DESIGN**

Due to the approval of post-first-line regimens and a lower than anticipated accrual rate, the design of the study has been modified. First, the primary endpoint has been changed from OS to PFS to reflect PFS as a relevant endpoint, which also results in a reduction in sample size. In addition, a hard-stop on accrual at a specific time point, even if the accrual target is not met, has been imposed. The following sections lay out the specific details for this new design.

The original design specifies that the Phase II interim analysis to evaluate for stopping for futility will be performed when 64 progression events have been observed, at which time it is expected that 212 eligible patients will have been accrued. In the new design, the sample size for this study has been reduced to the anticipated Phase II sample size of 212 patients with a hard stop in accrual on October 1, 2018, if the accrual to the study has not reached 212 patients.

The primary objective for the new design is to compare PFS between the arms at the 1-sided 0.025 level. This analysis would take place when 134 PFS events or 70% of the events among eligible patients have been observed (whichever comes first and will depend on sample size attained). With 134 PFS events, this study has 90% power to detect a hazard ratio of 0.57 (75% improvement). The following table describes the analysis as a function of how many patients are accrued by the time of study closure:

Final Sample Size	# events at analysis	HR with 90% power	improvement in PFS
160	112	0.54	85%
180	126	0.56	78%
200	134	0.57	75%
212	134	0.57	75%

An interim analysis will take place when 64 PFS events have been observed. This analysis will be presented to the SWOG Data and Safety Monitoring Committee at the SWOG Group Meeting closest to this number of events. This analysis will evaluate if there is evidence to recommend early stopping of the study for futility by testing the null hypothesis at the 0.5 level, using a stratified log-rank test. If the p-value is 0.5 or greater, than the recommendation will be that there is insufficient evidence to continue accrual to this study.

Secondary Objectives under the revised design are to compare response rates, OS, time to treatment failure (TTF), time to treatment discontinuation (TTD), and toxicity.

Assuming 212 patients enrolled over 36 months with 14 months of additional follow-up, a one-sided log-rank test with an alpha of 0.025 has 90% power to detect an OS hazard ratio of 0.5, corresponding to a 2-fold increase in median OS, under the exponential distribution. Similarly, if it is assumed that the median TTF is 11 months, and the median TTD is also 11 months, there will be 92% power to detect a 70% increase in medians (hazard ratio of 0.59) for each of these endpoints.

Assuming 85% of patients will have measurable disease, 180 patients will be evaluable for the response comparison between arms. Response rates between the arms will be compared using a chi-squared test of independence at the 1-sided 5% level. With 90 patients per arm, this design has 93% power to detect at least a 22% difference in response rates between the arms and within each arm the rates can be estimated to within 10% with 95% confidence.

Toxicity rates between arms will be assessed using a chi-squared or Fisher's exact test (as appropriate) at the 1-sided 5% level. Assuming all eligible patients are evaluable for toxicities, rates can be estimated to within 10% with 95% confidence and any toxicity with at least 5% prevalence has almost a 100% chance of being observed. With 106 patients per arm, this design has 92% power to detect at least a 20% difference between the arms.

d. Secondary Objectives

Additional analyses will be to compare response rates, OS, time to treatment failure (TTF), time to treatment discontinuation (TTD), and toxicity.

Assuming 212 patients enrolled over 36 months with 14 months of additional follow-up, a one-sided log-rank test with an alpha of 0.025 has 90% power to detect a OS hazard ratio of 0.5, corresponding to a 2-fold increase in median OS, under the exponential distribution. Similarly, if it is assumed that the median TTF is 11 months, and the median TTD is also 11 months, there will be 92% power to detect a 70% increase in medians (hazard ratio of 0.59) for each of these endpoints.

Assuming 85% of patients will have measurable disease, 180 patients will be evaluable for the response comparison between arms. Response rates between the arms will be compared using a chi-squared test of independence at the 1-sided 5% level. With 90 patients per arm, this design has 93% power to detect at least a 22% difference in response rates between the arms and within each arm the rates can be estimated to within 10% with 95% confidence.

Toxicity rates between arms will be assessed using a chi-squared or Fisher's exact test (as appropriate) at the 1-sided 5% level. Assuming all eligible patients are evaluable for toxicities, rates can be estimated to within 10% with 95% confidence and any toxicity with at least 5% prevalence has almost a 100% chance of being observed. With 106 patients per arm, this design has 92% power to detect at least a 20% difference between the arms.

11.3 Accrual

The estimated accrual rate is 5-6 patients per month with an assumed 5% ineligibility rate, which will provide the total goal of 223 patients over a 36 month period. However, there will be a hard stop on accrual on October 1, 2018, even if the accrual goal of 212 eligible patients has not been met. In addition, if the study has not accrued 173 patients by April 14, 2018 (the SWOG Spring 2019 meeting), then the study will be closed to further accrual.

11.4 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports

every 6 months from the SWOG Statistics and Data Management Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

This section does not apply to this protocol.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than 14 calendar days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored clinical trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

b. CTSU Registration Procedures

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

1. **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: the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

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.

2. **Downloading Site Registration Documents:**

Site registration forms may be downloaded from the **S1403** 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 SWOG link to expand, then select trial protocol **S1403**.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. **Requirements For S1403 Site Registration:**

- CTSU Transmittal Sheet (optional)
- 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)

4. **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

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

5. **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 at the top of your screen
- 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 as 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.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

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://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

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 and, upon enrollment, initializes the patient in the Rave database. 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. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino

- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

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

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

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

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. 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, you must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

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 that have not previously activated their iMedidata/Rave account at the time of initial 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 888/823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF INITIAL REGISTRATION, SUBMIT:

S1403 Onstudy Form

Baseline Tumor Assessment Form (RECIST 1.1)

Smoking Status Assessment Form

Radiology reports from all scans performed to assess disease at baseline

Pathology report from initial diagnosis

Pathology report from a CLIA-certified lab documenting presence of a sensitizing EGFR mutation

S1403 Local Pathology Review Form (see Section 18.3)

NOTE: Upload radiology reports, pathology reports, and the S1403 Local Pathology Review Form via the Source Documentation: Baseline form in RAVE®.

b. SUBMIT:

Specimens as specified in Section 15.0

c. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT (1 CYCLE = 28 DAYS), SUBMIT:

S1403 Treatment Form

S1403 Adverse Event Form

d. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT (SEE STUDY CALENDAR FOR SCHEDULE) UNTIL PROGRESSION (AS DEFINED IN SECTION 10.2e), SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease*. Physician must note tumor measurement in patient records.

*NOTE: Upload reports via the Source Documentation: Follow-up form in RAVE®

e. WITHIN 7 DAYS OF DISCONTINUATION OF PROTOCOL TREATMENT, SUBMIT:

Off Treatment Notice

S1403 Treatment Form

S1403 Adverse Event Form

Smoking Status Assessment Form

f. WITHIN 14 DAYS OF PROGRESSION OR RELAPSE, SUBMIT:

NOTE: IF PATIENT REMAINS ON TREATMENT FOLLOWING PROGRESSION (SEE SECTION 7.6a, CONTINUE TO SUBMIT THE S1403 ADVERSE EVENT FORM AND S1403 TREATMENT FORM AFTER EVERY CYCLE OF TREATMENT AS OUTLINED IN SECTION 14.4c).

Follow-Up Tumor Assessment Form (RECIST 1.1)

Site(s) of Progression/Relapse Form

Radiology reports from all scans performed to assess disease. Physician must note tumor measurement in patient records.

NOTE: Upload reports via the Source Documentation: Follow-up form in RAVE®.

g. ONCE OFF ALL PROTOCOL TREATMENT SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS AND THEN AT THE END OF YEAR 3:

Advanced NSCLC Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Notice of Death

If patient was still on treatment, submit materials specified in Section 14.4e; otherwise, submit Advanced NSCLC Follow-Up Form.

15.0 SPECIAL INSTRUCTIONS

15.1 General specimen submission instructions

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system.

General instructions for specimen collection, processing, labeling, packaging, and using the online Specimen Tracking system can be accessed on the SWOG Specimen Submission webpage for solid tumor studies, located at the following URL:

http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp.

Specimens will be used for the purposes described in Section 18.1.

15.2 Whole blood

The submission of whole blood is required for all patients.

Immediately after IRB approval of this protocol, sites must contact Guardant Health Client Services to order kits, as follows:

- Phone Guardant Health Client Services at 888/698-8887 or send email to clientservices@guardant health.com.
- Site must identify itself as a participant in the SWOG study **S1403**.
- Provide the following information:
  - Treating physician's name
  - Treating physician's email address
  - Contact name
  - Contact email address
  - Contact phone
  - Address to which kits should be sent
  - Number of kits needed (three kits are recommended as a starter supply)

Kits will arrive within 72 hours after ordering (excluding weekends and holidays).

Kits include two Streck Cell-Free DNA blood collection tubes, collection instructions, FedEx return bags, and pre-printed FedEx airway bills. Blood collection tubes must be used before their expiration date.

Collect blood at the following three time points:

- pre-treatment
- Cycle 3 visit
- progression (at the time when progressive disease by RECIST criteria is documented or any time point thereafter if the patient continued treatment post-progression)

Draw 10 mL of blood in each of the two tubes provided and process as per the instructions in the kit. Include the patient initials and SWOG patient ID on each tube.

Ship to Lab #220 (Guardant Health - see the Specimen Tracking System) via FedEx Priority Overnight.

15.3 Buffy coat and plasma:

The submission of buffy coat and plasma is required for all patients. Kits are not provided for these specimens.

Collect blood at the following three time points:

- pre-treatment
- Cycle 3 visit
- progression (at the time when progressive disease by RECIST criteria is documented or any time point thereafter if the patient continued treatment post-progression)

Draw approximately 10 mL blood in 1-2 lavender (EDTA) tubes. Blood should be placed on wet ice immediately after collection and processed as soon as possible (preferably within 2 hours). Centrifuge vacutainer tubes at approximately 800 x g for 10 minutes (preferably in a refrigerated centrifuge, if available). Immediately after centrifugation, carefully transfer plasma to a new 15 mL conical tube using a pipette and being careful not to aspirate the interface between the plasma and the platelets (buffy coat layer). Set aside original purple top tubes for later processing. Then centrifuge plasma a second time at 1200 x g for 10 minutes. After the second centrifugation, aliquot plasma in 500 mcl aliquots into 6-10 labeled 1.8-2.0 ml cryovials, being careful not to disturb the pellet in the bottom of the tube. The buffy coat, a whitish layer of cells between the plasma and red blood cell layers, should be collected from the original purple top tube(s) and transferred into 2 labeled 1.8-2.0 ml cryovials (contamination with RBC not a concern). Freeze cryovials immediately and store at or below -70° until shipped to the SWOG Specimen Repository on dry ice.

Samples may be batch shipped. **Ship to Lab #201** (SWOG Specimen Repository - Solid Tissue, Myeloma and Lymphoma Division - see the Specimen Tracking System).

15.4 Prestudy tissue

The submission of tissue is required for all patients. Submit within 28 days after registration. Kits are not provided for these specimens.

Submit one or two paraffin-embedded tissue blocks containing formalin fixed tumor and corresponding hematoxylin and eosin (H&E) slide. Submission of blocks is strongly encouraged. However, if blocks are unavailable, 15-20 unstained slides are acceptable alternatives (12 absolute minimum, 20 strongly encouraged). Cytology (e.g. fine-needle aspirations, pleural effusion specimens) can be accepted only if they are paraffin embedded as cell blocks, positive for malignant cells, and provide sufficient number of required blocks or slides.

Tumor material must be reviewed by a local pathologist to ensure at least 100 viable tumor cells are present in the sample (the estimate must be noted in the **S1403** Local Pathology Review Form [Section 18.3]). The local pathologist must review and sign the **S1403** Local Pathology Review Form. The **S1403** Local Pathology Review Form and pathology report must be submitted with the specimen to the SWOG Solid Tumor Repository and must be uploaded via the Source Documentation: Baseline in Rave®.

If a new biopsy is necessary at baseline due to insufficient tissue, in addition to the requisite formalin-fixed paraffin embedded tissue, a portion of the biopsy should be retained as fresh-frozen tissue, if feasible. Tissue (e.g. 1-2 cores, pleural effusion cell pellets, bronchoscopy forcep biopsies, etc.) should be immediately flash frozen in liquid nitrogen and stored at -80°C until shipped on dry ice.

Refer to the general labeling, packaging, and shipping instructions at http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp and **ship to Lab #201** (SWOG Specimen Repository - Solid Tissue, Myeloma and Lymphoma Division - see the Specimen Tracking System).

15.5 Additional requirements for sites participating in the repeat biopsy study, *but not* in the patient-derived xenograft (PDX) study

This section only applies to those sites participating in the repeat biopsy study, but not in the patient-derived xenograft (PDX) study. For a list of these sites, please refer to the Activation notice distributed April 1, 2015 and any subsequent memoranda.

Kits are not provided for these specimens.

Specimens must be submitted at disease progression for all patients who had a treatment response. Treatment response is considered either an objective response (complete or partial response) or stable disease > 6 months. The repeat biopsy can be performed at any time point after the initial disease progression if the patient continued treatment post-progression. A repeat biopsy can also be performed at progression even for patients who have previously discontinued treatment (i.e. for toxicity). Once the patient discontinues treatment following progression, the repeat biopsy should be performed within 30 days. The biopsy site should be chosen based on safety and should preferably be from an area of tumor growth.

Submit one or two paraffin-embedded tissue blocks containing formalin fixed tumor and corresponding hematoxylin and eosin (H&E) slide. Submission of blocks is strongly encouraged. However, if blocks are unavailable, 15-20 unstained slides are acceptable alternatives (12 absolute minimum, 20 strongly encouraged). Cytology (i.e. fine-needle aspirations, pleural effusion specimens) can be accepted only if they are paraffin embedded as cell blocks, positive for malignant cells, and provide sufficient number of required blocks or slides.

Frozen tissue should also be obtained if sufficient material exists. Tissue (e.g. 1-2 cores, pleural effusion cell pellets, bronchoscopy forcep biopsies, etc.) should be immediately flash frozen in liquid nitrogen and stored at -80°C until shipped on dry ice.

Priority should be given to FFPE preparation. If more than 2 cores (or equivalent) are collected, tissue should be apportioned as follows: half of the specimen should be formalin-fixed and paraffin-embedded, and the remaining should be frozen. If ≤ 2 cores (or equivalent) are obtained, all material should be FFPE.

Tumor material must be reviewed by a local pathologist to ensure at least 100 viable tumor cells are present in the sample (the estimate must be noted in the **S1403** Local Pathology Review Form [Section 18.3]). The local pathologist must review and sign the **S1403** Local Pathology Review Form. The **S1403** Local Pathology Review Form and pathology report must be submitted with the specimen to the SWOG Solid Tumor Repository and must be uploaded via the Source Documentation: Baseline in Rave®.

Refer to the general labeling, packaging, and shipping instructions at http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp and **ship to Lab #201** (SWOG Specimen Repository - Solid Tissue, Myeloma and Lymphoma Division - see the Specimen Tracking System).

15.6 Additional requirements for sites participating in the repeat biopsy study *and* the patient-derived xenograft (PDX) study

This section only applies to those sites participating in the repeat biopsy study and the patient-derived xenograft (PDX) study. For a list of these sites, please refer to the Activation notice distributed April 1, 2015 and any subsequent memoranda.

Kits are not provided for these specimens.

Specimens must be submitted at disease progression for all patients who had a treatment response. Treatment response is considered either an objective response (complete or partial response) or stable disease > 6 months. The repeat biopsy can be performed at any time point after the initial disease progression if the patient continued treatment post-progression. A repeat biopsy can also be performed at progression even for patients who have previously discontinued treatment (i.e. for toxicity). Once the patient discontinues treatment following progression, the repeat biopsy should be performed within 30 days. The biopsy site should be chosen based on safety and should preferably be from an area of tumor growth.

Please note that there are two different receiving labs listed below: one for fresh tissue and one for FFPE and frozen tissue.

1. Fresh tissue

   Since the fresh tissue will be implanted into mice, biopsies should be performed on Monday, Tuesday, Wednesday, or Thursday. If performed on Friday, fresh tissue need not be collected.

   a. The physician should obtain the maximum amount of tumor that is prudent at the time of biopsy or resection. Minimum sample size is a core measuring 8mm x 3mm. Please approximate these dimensions.

   b. The specimen should be collected following Institution Universal precautions SOPs for maintaining tissue integrity. Please remind all personnel that are involved in processing the sample that it will be implanted in profoundly immune deficient mice, so it is imperative that extra care be taken in sample collection to minimize the risk of transferring human bacteria to the mice.

   c. The tumor sample should be placed in a 50 ml screw cap conical tube containing 40 ml RPMI buffer (without fetal calf serum), preferably within 30 minutes of tumor removal. Seal cap tightly with Parafilm. Sample should be refrigerated at 4°C until packed for shipping on the same day as procurement.

d. The sealed conical tube containing RPMI and the tumor specimen must be wrapped in absorbent material (i.e. paper towels) and placed in an airtight plastic bag (i.e. a resealable bag). Pack the specimen into an insulated Styrofoam shipper with a refrigerated (4° C) cool pack (not frozen) to protect specimen from temperature fluctuations. All paperwork pertaining to the patient should be placed in a plastic bag, sealed tightly, and packed with the tissue shipment. Include the Jackson Laboratory Sample Submission Form (Section 18.4).

e. Prior to shipping, contact Margaret Bundy at 916-469-2609. **Ship to Lab #216** (The Jackson Laboratory - see the Specimen Tracking System).

2. Paraffin-embedded and frozen tissue

Submit one or two paraffin-embedded tissue blocks containing formalin fixed tumor and corresponding hematoxylin and eosin (H&E) slide. Submission of blocks is strongly encouraged. However, if blocks are unavailable, 15-20 unstained slides are acceptable alternatives (12 absolute minimum, 20 strongly encouraged). Cytology (i.e. fine-needle aspirations, pleural effusion specimens) can be accepted only if they are paraffin embedded as cell blocks, positive for malignant cells, and provide sufficient number of required blocks or slides.

Frozen tissue should also be obtained if sufficient material exists. Tissue (e.g. 1-2 cores, pleural effusion cell pellets, bronchoscopy forcep biopsies, etc.) should be immediately flash frozen in liquid nitrogen and stored at -80°C until shipped on dry ice.

Priority should be given to FFPE preparation. If more than 2 cores (or equivalent) are collected, tissue should be apportioned as follows: half of the specimen should be formalin-fixed and paraffin-embedded, and the remaining should be frozen. If ≤ 2 cores (or equivalent) are obtained, all material should be FFPE.

Tumor material must be reviewed by a local pathologist to ensure at least 100 viable tumor cells are present in the sample (the estimate must be noted in the **S1403** Local Pathology Review Form [Section 18.3]). The local pathologist must review and sign the **S1403** Local Pathology Review Form. The **S1403** Local Pathology Review Form and pathology report must be submitted with the specimen to the SWOG Solid Tumor Repository and must be uploaded via the Source Documentation: Baseline in Rave®.

Refer to the general labeling, packaging, and shipping instructions at http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp and **ship to Lab #201** (SWOG Specimen Repository - Solid Tissue, Myeloma and Lymphoma Division - see the Specimen Tracking System).

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the SWOG Operations Office by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in this study are afatinib and cetuximab. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Afatinib and Cetuximab

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [Section 16.1f.]

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a Non-CTEP IND:**

1. **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Statistics and Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

g. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss**. Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.**

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal.** "Death neonatal" is defined in CTCAE as "Newborn death occurring during the first 28 days after birth." A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

17.0 BIBLIOGRAPHY

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18.0 APPENDIX

18.1 Translational Medicine

The primary translational objectives of this study are to understand mechanisms of sensitivity and resistance to afatinib plus cetuximab and afatinib alone in the front-line treatment setting in patients with *EGFR* mutation positive lung cancer. The goals are to study pre-treatment tumor samples (required from all patients on the trial) to understand mechanisms of sensitivity to these agents and to compare pre-treatment and repeat biopsy specimens at progression (obtained from a subset of patients on the trial at specific designated institutions as discussed below) to investigate the molecular mechanisms of resistance to these drugs and to devise strategies to overcome them. See Section 15.0 for details regarding tissue collection.

All patients enrolled in the therapeutic trial will be eligible for these studies. *Pre-treatment* specimens will have been processed as per standard of care for formalin fixation and paraffin-embedding at individual institutions and are required for enrollment on the trial. Submission of a *repeat biopsy* specimen at progression on afatinib plus cetuximab or afatinib alone will be required at only a subset of institutions participating in the Repeat Biopsy Sub-Study. Our goal is to collect repeat biopsies from 100 patients (approximately 50 patients on each arm of the study). In cases with limited tissue, priority will be given to studies as listed in order below (i.e. EGFR T790M testing will have highest priority, then copy number alterations, etc.).

The translational medicine studies proposed are described below ***in order of priority***.

a. **EGFR T790M mutation analysis (INTEGRATED)**

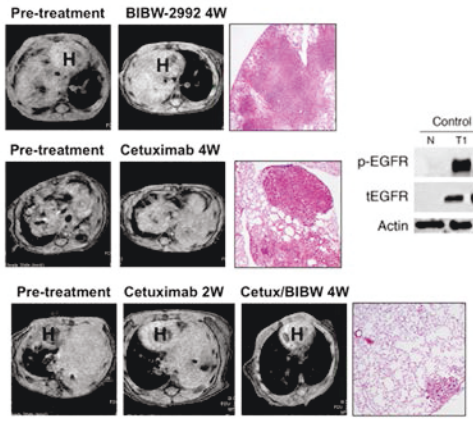

Figure 1. The combination of afatinib+cetuximab leads to regression of EGFRL858R+T790M-induced tumors in genetically engineered mouse models. (A) Magnetic resonance images and histopathology of lungs from mice treated with afatinib (BIBW2992) alone (top), cetuximab alone (middle) or afatinib+cetuximab (bottom). (B) Western analysis of tumors from mice treated with afatinib (B), cetuximab (C) or the combination of both agents (B+C) for phosphorylated and total EGFR. Figure adapted from reference 11.

Background, hypotheses and objectives: In *EGFR* mutant lung adenocarcinomas, resistance to EGFR TKIs is most frequently associated (50-60% of cases) with the emergence of a secondary mutation in *EGFR*: the *EGFR* T790M mutation. Using tetracycline inducible transgenic mouse models of *EGFR* mutant lung cancer harboring the erlotinib-resistant T790M mutation, it has been shown that that combined treatment with the irreversible TKI, afatinib, and the antibody to EGFR, cetuximab, caused these tumors to

regress dramatically whilst neither drug alone was effective (Figure 1). *(1)*

This preclinical study led to a Phase Ib/II clinical trial of these two agents in *EGFR* mutant NSCLC with acquired resistance to first generation TKIs. Tumors in approximately 30% of patients responded to these agents in combination. *(2)* Preliminary data from this trial suggests that there is benefit for patients both harboring and lacking T790M. In contrast, afatinib alone, cannot overcome T790M-mediated resistance in preclinical models and in patients.

The prevalence of the *EGFR* T790M mutation in lung adenocarcinoma tumors harboring EGFR TKI sensitizing mutations prior to treatment with an EGFR TKI is unclear with reports ranging from 0-35%. *(3,4,5,6,7,8)* It is likely, from evidence available to date, that the presence of pre-existing T790M will negatively influence the outcome to treatment with afatinib but NOT afatinib plus cetuximab. Knowledge of the *EGFR* T790M status in patients prior to treatment is therefore essential for us to determine whether this subset of patients responds differently to afatinib plus cetuximab or afatinib alone. ***Specifically, we will test the hypothesis that the presence of pre-existing T790M will negatively influence the outcome to treatment with afatinib but NOT afatinib plus cetuximab.***

Preliminary Data: Preliminary data from the trial of the combination of afatinib plus cetuximab in patients with acquired resistance to a 1st-generation TKI (erlotinib or gefitinib) suggests that there is benefit for patients both harboring and lacking T790M (see above). ***We, therefore anticipate that the emergence of the EGFR T790M mutation will not be a major contributor to resistance to combination therapy.*** In contrast, we expect that the T790M mutation will emerge in approximately 50% of patients treated with afatinib alone as is seen in patients treated with other single-agent TKIs.

Research Design and Methods: Using a sensitive pyrosequencing assay to measure the *EGFR* T790M mutation (and the original sensitizing mutation), we will test whether the presence of a baseline *EGFR* T790M mutation is correlated with clinical benefit from afatinib plus cetuximab or afatinib alone. This same assay will be used to test whether the *EGFR* T790M mutation emerges during treatment by analyzing post-treatment re-biopsy specimens from patients on both treatment arms. We will also allow quantitatively assess whether the ratio of sensitizing *EGFR* mutation (*EGFR*s) to *EGFR* T790M influences outcome and is altered during treatment. This assay will be performed in the CLIA-certified Yale Cancer Center Tumor Profiling lab by Zenta Walther on DNA extracted from formalin-fixed paraffin embedded material. **The assay is used routinely for clinical purposes at Yale.** Next generation sequencing approaches for the detection and quantification of *EGFR* mutations will also be used. Tissue submission and T790M results will be monitored on an on-going basis to ensure adequate tissue submission is occurring. We anticipate requiring ~5 unstained tissue sections for this study.

Zenta Walther is the key contact for questions regarding this translational medicine study:

Zenta Walther
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Statistical Design:

1. **Evaluate if the presence of de novo EGFR T790M mutation or other molecular alterations in pre-treatment tissue are associated with clinical outcomes.**

Conservatively assuming ~20% of patients will not have baseline assay results due to either assay failure or unusable specimens, we expect assay results from 460 patients at baseline (approximately 230 per arm). With 460 patients, the prevalence of T790M and of the other discrete molecular alterations can be estimated to within 5% with 95% confidence. The probability that at least one T790M mutation is observed assuming the true prevalence is at least 2% is almost 100% (>99%).

To evaluate if the presence of de novo T790M mutation is associated with primary resistance to afatinib, PFS and OS will be compared between T790M mutation positive and negative patients randomized to the afatinib monotherapy arm using a logrank test stratified by EGFR mutation status (exon 19 deletion vs L858R mutation). Assuming a two-sided alpha of 0.10, the power to detect a 2-fold difference in median OS and PFS, under various scenarios is as follows:

prevalence of de novo T790M mutation	OS HR=0.5	PFS HR=0.5
5%	65%	73%
10%	88%	93%
15%	95%	98%
20%	98%	99%

To evaluate the hypothesis that pre-existing T790M is negatively associated with absolute difference in PFS (and OS) among patients randomized to receive afatinib monotherapy a test of interaction will be performed at the 1-sided 20% level. Assuming the prevalence of the mutation is 20%, the overall treatment hazard ratio is 0.50, the median PFS for afatinib-treated patients with and without the mutation is 6 and 12 months, respectively; and assuming that the true treatment hazard ratio is .34 (a 2.94. fold improvement in median PFS) among T790M patients and the true treatment hazard ratio is .54 (an 85% improvement in median PFS) among patients without the mutation, then this design has 83% power to detect a difference in PFS hazard ratios.

Although preliminary data show a numerical difference in median PFS between patients with exon 19 deletions versus L858R mutations, the difference was not statistically significant. Nevertheless, we will investigate whether de novo T790M mutations are associated with either mutation, using a two-sided Fisher's exact test, and whether there is any difference between these groups. In addition, we will estimate median PFS within each group separately.

To evaluate if the presence of de novo T790M mutation is associated with sensitivity to afatinib plus cetuximab or afatinib alone the response rate will be compared between T790M mutation positive and negative patients using a one-sided Fisher's exact test at the 5% level. Assuming 85% of patients will have measureable disease, then 391 patients will be

included in the analysis of response. This design has at least 89% power to detect a 20% difference in response rates between T790M mutation positive and negative patients assuming the prevalence of the T790M mutation is 20%.

2. **Investigate whether the ratio of sensitizing EGFR mutation to EGFR T790 mutation is related to clinical outcomes**.

To evaluate if the ratio of EGFR sensitizing mutation to EGFR T790M mutation (EGFRs/EGFR T790M) among patients with T790M is predictive for afatinib monotherapy, analyses will be performed in a similar fashion to the evaluation of T790M among patients with measurable T790M (which defines T790M). Cox regression will be used to assess the predictive association of the ratio in the afatinib monotherapy arm with both OS and PFS. Further analyses will evaluate a differential effect by including an interaction term for treatment x EGFRs/EGFR T790M ratio among all patients randomized to either afatinib plus cetuximab or afatinib alone with EGFR T790M.

3. **Compare the ratio of sensitizing EGFR mutation to EGFR T790 mutation between tissue collected at re-biopsy after progression to baseline.**

To evaluate if EGFRs/EGFR T790M is lower at progression than in pre-treatment specimens among patients with results available for pre-treatment and progression, a one-sample t-test (or Wilcoxon signed-rank test) will be used to test the null hypothesis that the difference between the progression ratio and the pre-treatment ratio (or an appropriate transformation of the difference, determined after exploratory data analysis) is greater than zero in favor of the alternative that the difference is less than zero.

We will evaluate the emergence of EGFR T790M mutations in patients who progress after an initial response to treatment (defined as complete or partial response or stable disease for ≥ 6 months). Post-treatment tissue specimens will be collected on 100 patients, approximately 50 on each treatment arm, and it is assumed that at most 35% of these patients will have a T790M mutation at baseline. It is further assumed that approximately 50% of patients on the single agent afatinib arm will have developed T790M mutations at the time of resistance. Thus, if we assume approximately 33 patients per arm, using a binomial test of proportions with a one-sided alpha of 0.10, there will be at least 80% power (depending on the de novo prevalence) to detect a difference of 30% between treatment arms.

b. **Copy number alterations in *MET*, *EGFR* and *HER2* (INTEGRATED)**

Background, hypotheses and objectives: Resistance to EGFR TKIs is most frequently associated (50-60% of cases) with the emergence of the *EGFR* T790M mutation. *(9)* In addition, bypass mechanisms that activate parallel or downstream signaling pathways such as ***amplification of the receptor tyrosine kinase (RTK) genes MET and HER2***, activation of AXL or mutations in *PIK3CA* and *BRAF* have also been observed in the setting of TKI resistance. *(10,11,12,13,14,15,16)* Moreover, amplification of the *EGFR* allele harboring the T790M mutation was observed in a subset of TKI-resistant *EGFR* mutant lung

adenocarcinomas. *(17)* In view of the evidence implicating *MET*, *HER2* and *EGFR* in resistance to first generation TKIs, ***we hypothesize that amplification of the receptor tyrosine kinases, EGFR, HER2 and MET may contribute to both decreased sensitivity and acquired resistance to afatinib plus cetuximab and afatinib alone.*** Moreover, since these drugs target *EGFR* (afatinib and cetuximab) and *HER2* (afatinib), it is likely that tumor escape mechanisms will involve these receptors in at least a fraction of cases.

Our **objective** is to determine if amplification of the receptor tyrosine kinases, *EGFR*, *HER2* and *MET* contributes to both decreased sensitivity and acquired resistance to afatinib plus cetuximab and afatinib alone.

Preliminary Data: Data in the literature support the role of amplification of these receptor tyrosine kinases as indicated above. Moreover, unpublished data from our analyses of repeat biopsies with resistance to EGFR-directed therapies (including afatinib plus cetuximab) at Yale, has uncovered amplification of these RTKs.

Research Design and Methods: Pre- and post-treatment tissue will be analyzed for alterations in *MET*, *EGFR* and *HER2* using Fluorescence In Situ Hybridization (FISH) performed by the CLIA-certified Yale Cancer Center Molecular Diagnostics Laboratory by Minhong Wan in formalin-fixed paraffin embedded (FFPE) tissues at baseline and at the time of acquired resistance to afatinib plus cetuximab or afatinib alone (the former only for the 100 patients on the repeat biopsy portion of the study). The following probe sets will be used for these studies:

a. *MET* gene (FISH analysis): C-MET (7q31)/SE7 probe (Cat# KI-10719, Kreatech, Durham, NC).

b. *HER2* gene (FISH analysis): Vysis_PathVysion™ HER-2 DNA Kit (Cat# 02J01-036, Abbott Laboratories, Abbott Park, Illinois).

c. *EGFR* gene (FISH analysis): EGFR, HER-1 (7p11)/SE7 probe (Cat# KI-10702, Kreatech, Durham, NC).

For copy number analysis of *EGFR*, *MET* and *HER2*, two 5um sections mounted on charged slides will be used for each FISH assay (a total of 6 slides pre-treatment and 6 slides from the re-biopsy at progression). The ratio of specific gene signals to centromeric probe signals will be used to calculate copy number. For all three genes, a ratio >2.0 is interpreted as amplification of the gene if at least 50 nuclei are counted based on current literature. *(18,19,20,21)*

Minhong Wan is the key contact for questions regarding this translational medicine study:

Minhong Wan
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Statistical Design:

1. To evaluate the prognostic role of these molecular alterations (e.g. *MET*, *EGFR* or *HER2* amplification) for *resistance* to afatinib plus cetuximab or afatinib alone.

   For each potential marker, a logrank test at the 5% level will be used to compare OS and PFS between patients with amplification versus patients without amplification. The following table details the power to detect a two-fold difference in median PFS using a 2-sided 0.10 level logrank test across a range of possible marker prevalence.

Marker prevalence	Power
5%	73%
10%	93%
15%	98%
20%	99%

   HER2 amplification is expected to be seen in approximately 1% and *MET* amplification in 3% of patient specimens at baseline. The relationship between OS, PFS and these abnormalities will be evaluated as above, although the power to detect differences is expected to be low.

   Further comparisons will be performed within treatment arms. To assess a differential effect by treatment arm, Cox regression will be used to test treatment interaction, again using OS and PFS as the outcome.

   To evaluate the prognostic role of other molecular alterations (e.g. *MET*, *EGFR* or *HER2* amplification) for *sensitivity* to afatinib plus cetuximab or afatinib alone, for each potential marker, a chi-squared or Fisher's exact test at the 5% level will be used to compare response rates between patients with amplification versus patients without amplification.. The following table details the power to detect a 30% difference in response rates using a 1-sided 0.05 level test across a range of possible marker prevalence.

Marker prevalence	Power
5%	46%
10%	76%
15%	90%
20%	95%

2. **Compare copy number alterations in MET, EGFR, and HER2 between tissue specimens collected after disease progression and pretreatment tissue specimens**

Pre- and post-treatment tissue will be analyzed for alterations in *MET*, *EGFR* and *HER2* using Fluorescence in situ Hybridization (FISH) among those patients who progress after an initial response. *EGFR*, *MET*, and *HER2* amplification in patients with acquired resistance are expected in approximately 5%, 5%, and 12% of cases, respectively. For each of these markers, a one-sample t-test (or Wilcoxon signed-rank test) will be used to test the null hypothesis that the absolute difference between the copy number after progression and the copy number in the pre-treatment specimen (or an appropriate transformation of the difference, determined after exploratory data analysis) is not equal to zero.

c. **Whole exome sequencing of pre- and post-treatment specimens (INTEGRATED).**

Background, Hypotheses and Objectives: Although the major mechanisms of resistance to EGFR inhibitors have been identified and we will establish their incidence and relationship with response to therapy as described above, other known and unknown mechanisms of resistance also occur and many of these are mutationally driven. Moreover, co-occurring mutations also occur with EGFR mutations and little is known about how these affect response to therapies. For example, mutations in tumor suppressors like TP53 occur in >50% of EGFR mutant tumors. Tumors that do not have TP53 mutations however, have mutations in other tumor suppressor genes such as ATM, CDKN2B and RB1. The data that we collect from whole exome sequencing of these tumors at baseline and upon the emergence of drug resistance provide us with the unique opportunity to analyze the relationship between co-occurring mutations, response to therapy and drug resistance. The objectives of this analysis are to: 1) identify genes that when mutated modulate the response to EGFR inhibitors either by affecting response rates, PFS or OS and 2) identify genes that are mutated in tumors that have acquired resistance to either afatinib plus cetuximab or afatinib alone. We hypothesize that: 1) tumors with mutations in TP53 at baseline will have a worst outcome compared to those with intact TP53, 2) mutations in genes that are rarely observed as a mechanism of resistance to erlotinib like *PIK3CA*, *NRAS* and *BRAF* will be detected more frequently in tumors with acquired resistance to afatinib plus cetuximab compared to afatinib alone. In addition, to testing these specific hypotheses, the whole exome sequencing data will allow us to identify novel genes and pathways that may play a role in response and resistance to these drugs.

Preliminary Data: To identify new mechanisms of resistance and understand the genomic complexity and evolution of *EGFR* mutant tumors, we have performed whole exome sequencing (WES) of 22 pre- and post-treatment specimens from patients with *EGFR* mutant lung cancer. The mean number of treatment-acquired mutations in these samples was 26 (range 0-94). Non-synonymous mutations in cancer genes (defined by the Cancer Gene Census) were enriched in resistant tumors compared to pre-treatment specimens. Mutations in cancer genes were more frequently retained in the post-treatment specimens compared to non-cancer genes suggesting that the former are undergoing selection in the presence of drugs. These preliminary studies highlight the feasibility of obtaining, performing and analyzing WES from lung cancers before and at resistance to EGFR TKIs.

Research Design and Methods: The Nimblegen/Roche solution-capture exome array will be used for exome capture followed by sequencing on the Illumina HiSeq platform. This technology is routinely used on FFPE material at the Yale Center for Genome Analysis. This analysis will utilize FFPE and frozen tissue.

Statistical Design: The evaluation of each mutated gene's prognostic value will be analyzed in a similar fashion as described in section b above. Since the number of genes investigated may be large, an adjustment for multiple comparisons (e.g. Bonferroni) will be employed.

To assess whether mutations in will be detected more frequently in tumors with acquired resistance to afatinib plus cetuximab compared to afatinib alone, exact 95% confidence intervals will be constructed for the proportion of mutations observed on each arm. Assuming 50 patients per arm, the true proportion of patients with a specific mutation can be estimated to within at least 14%.

d. **EGFR Immunohistochemistry (INTEGRATED)**

Background, hypothesis, objective and preliminary data: EGFR Protein expression assessed by IHC related to cetuximab therapy was studied in the FLEX-study, where chemotherapy was compared to chemotherapy + cetuximab. While the overall OS for the "unselected" group of advanced NSCLC patients was modestly significant with HR= 0.87 (0.76-0.99, p=0.04), the EGFR IHC high expressing group showed HR=0.73, p=0.001,, median OS: 12.0 months (+cetuximab) versus 9.6 months (- cetuximab), and for the Caucasian population (majority of patients): OS HR=0.64 (0.49-0.83). The scoring system was well validated and cut-off for EGFR high expression was 200 or more. The principle of the protein expression assessment was described by Hirsch et al, J Clin Oncol 2003). Thus, we hypothesize that EGFR protein expression has a predictive association to cetuximab therapy in NSCLC, and needs to be included as an integrated biomarker for any cetuximab combination. It is also included as an integrated biomarker in the large prospective phase III cetuximab study performed by SWOG (S0819). The objective of this study is to evaluate the relationship between EGFR expression levels and sensitivity to afatinib plus cetuximab or afatinib alone.

In SWOG S1403 the H-score assessment of EGFR expression will be performed in Dr. Hirsch's lab, which is the lab that developed the H-score algorithm for EGFR.

Research Design and Methods: Immunohistochemistry evaluation of EGFR protein will be done in Dr. Hirsch's laboratory (CLIA certified) at the University of Colorado. Dr. Hirsch's lab has extensive experience with the H-score assessment of EGFR. *(30)* Two antibodies will be assessed; one targeting the external domain of the EGFR receptor (Dako) and another targeting the interior domain of the receptor (Ventana, 5 B7). The scoring system that will be used is the H-score ("Hybrid-score") in the range of 0-300.

Statistical Design:

It is assumed that IHC results will be obtained from 460 patients at baseline (approximately 230 per arm), and that among patients with an IHC result, 26% will be determined to be H-score positive (defined as an H-score > 200.

Within each arm we will investigate if H-score is prognostic for PFS, OS, or response, assuming no treatment effect, there will be approximately 91% power to detect a two-fold increase in median PFS for H-score positive patients using a logrank test with a one-sided alpha of 0.05. Furthermore, there will be approximately 89% power to detect a 2.5-fold increase in overall survival, using a stratified logrank test with a one-sided alpha of 0.05.Using a binomial test of proportions, there will be about 90% power to detect a 24% difference in response rates assuming a one-sided alpha of 0.05.

To evaluate the hypothesis that H-score positive status at baseline is associated with absolute difference in PFS (and OS) among patients randomized to receive afatinib monotherapy a test of interaction will be performed at the 1-sided 20% level. Assuming the overall treatment hazard ratio is 0.50, the median PFS for afatinib-treated patients who are H-score positive is 12 months and patients who are not H-score positive is 6 months and assuming that the true treatment hazard ratio is 0.4 (a. 2.5-fold improvement in median PFS) among H-score positive patients and the true treatment hazard ratio is 0.53 (an 89% improvement in median PFS) among patients who are not H-score positive, then this design has 64% power to detect a difference in PFS hazard ratios.

e. **Circulating DNA markers (INTEGRATED)**

Background, hypothesis, objective and preliminary data: Analysis of cfDNA (circulating free DNA) allows non-invasive assessment of gene mutations and copy number alterations to monitor patient tumor genetic evolution under selective pressure of treatment. Significant correlations between treatment-induced clearance of circulating tumor-derived DNA and outcomes have been noted, particularly with EGFR mutations in patients treated with EGFR TKIs. The objective of this study is to assess baseline, on-treatment and at-progression levels of circulating tumor DNA. We hypothesize that the levels of circulating tumor DNA (and associated EGFR mutations) will correlate with response to therapy (decrease) and resistance (increase).

Research Design and Methods: We will use a fully-validated, 68-gene panel (covering over 80,000 bases) consisting of actionable cancer-related genes, including all known EGFR mutations and deletions. Using Digital Sequencing Technology (DST) enables ultra-sensitive and ultraspecific detection of rare genomic abnormalities at the single molecule level, capable of detecting heterogenic DNA at a ratio of 0.1% of total DNA input. All work will be conducted in a CLIA- and CAP-certified laboratory. Levels of circulating tumor DNA will be estimated based on the allele frequency of mutant forms detected using the Guardant360 digital sequencing technology, built on a Illumina Hi-Seq 2500. This platform uses a paired-end sequence-by-synthesis approach coupled to customized bioinformatics that have been optimized to significantly reduce, if not eliminate, false positives. Digital sequencing libraries are prepared by tagging the nucleotide sequence with oligonucleotide descriptors, followed by amplification. Average coverage depths exceed 10,000. Additionally, detection of EGFR mutation variants in plasma will be also be performed using a Therascreen EGFR RGQ PCR kit (Qiagen), based on Scorpion-ARMS, under a modified protocol adapted for increased sensitivity in the evaluation of low-frequency

circulating tumor DNA. Results from the Scorpion-ARMS will serve as assay validation for the DST approach, and will ensure that all variants of the EGFR E19del are identified.

Statistical Design:

Tumor marker levels over time will be evaluated using a linear mixed model for continuous markers and using generalized estimating equations for binary markers.

f. **Patient-derived xenografts (tissue collection, INTEGRATED, see Section 15.6)**

Background: Patient-derived xenografts (PDXs) recapitulate the molecular, histological and treatment response profile of the original patient tumor. This enables the efficacy of modified or alternative therapies to be tested in a controlled, laboratory setting to identify regimens with enhanced activity and ability to overcome patient-specific resistance mechanisms emergent in the study population. Co-investigators at The Jackson Laboratory and UC Davis Comprehensive Cancer Center have a wealth of experience in establishing, maintaining and testing PDX models derived from NSCLC.

Research Design and Methods: We plan to establish patient-derived xenografts from fresh tumor samples collected at the time of acquired resistance to study therapy. At select institutions, fresh tumor specimens from biopsies at time of progression will be viably shipped overnight to the JAX-West facilities in Sacramento for implantation as per the established protocol.

A landmark analysis will be used to evaluate the correlation between post-randomization biomarker values and PFS and OS (from the landmark timepoint) using a Cox proportional hazards model.

Establishment of cell cultures and/or patient-derived xenografts from fresh samples collected at resistance (Jackson Laboratory). Tumor material will be used to establish PDX models from patients enrolled on this study. At select institutions, fresh tumor specimens from biopsies at time of progression will be viably shipped overnight to the JAX-West facilities in Sacramento for implantation as per the established protocol.

18.1 References

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18.2 Intake Calendar - Afatinib

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #S1403**

Institution/Affiliate _____ Physician _____

Treatment
Cycle #: _____ Start Date: _____ Start Day (Circle One): Sun M Tu W Th Fr Sat

Instructions for the participant:

Afatinib is a tablet you take once a day. This is a 28 day cycle calendar on which you are to put the date in the small box on the calendar and record the time you take your afatinib tablet (or the reason a dose was not taken) in the larger part of the box. Take the tablet as directed by the study doctor. Afatinib should be taken once a day on an empty stomach (i.e. one hour before or two hours after a meal). If you miss a tablet, take it as soon as you remember EXCEPT if your next scheduled dose is in less than 12 hours. In that case, just take the next tablet at your regular time. Tell your doctor about the medicine you take including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. If you develop any side effects from the afatinib tablet, mark this on the calendar on the day you note the effect. Be sure you have enough calendars to last until your next appointment. Bring your calendars and your pill container with leftover tablets with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: _____ **Year:** _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature: _____Date of CRA Review:_____

18.3 SWOG **S1403** Pathology Review Form

SWOG **S1403** Pathology Review Form
SWOG Solid Tumor Biorepository

SWOG ID #_____ Patient Initials: _____(L, FM)
Protocol of Interest: S1403

Pathology Diagnosis: _____

Please indicate time point:

□Baseline □Repeat biopsy after progression

Preliminary Data Specimen Submission:

□Resected Tissue □Core Biopsy □Fine Needle Aspiration (FNA)
□Effusion

Specimen Type Submitted:
□Block – Surgical Pathology Number* _____

□Slides – Surgical Pathology Number* _____

* This is **not** the number given to the specimen from the Specimen Tracking System.

Specimen Review

1) **Please confirm that a minimum of 12 unstained slides are available:**
Note: Submission of 1-2 paraffin-embedded blocks is strongly encouraged. However, if blocks are unavailable, 15-20 unstained slides are acceptable alternatives (12 slides is the absolute minimum).
□Adequate (≥ 12 slides) □Inadequate (<12 slides)

2) **Tumor Cells Available (PLEASE CHECK ONLY ONE)**:

□Adequate (≥100 cells) □Inadequate (< 100 cells)

_____ _____
Signature of Interpreting Pathologist Date

NOTE: A copy of this form is to be submitted along with the pathology report to the SWOG Solid Tumor Specimen Repository as outlined in Section 15.4.- 15,6, This form must also be uploaded via the Source Documentation: Follow-up in RAVE

Comments:

18.4 Jackson Laboratory Sample Submission Form

REQUISTION FORM: PATIENT DERIVED XENOGRAFT

Protocol Name: RANDOMIZED PHASE II TRIAL OF AFATINIB PLUS CETUXIMAB VERSUS AFATINIB ALONE IN TREATMENT-NAÏVE PATIENTS WITH ADVANCED, EGFR MUTATION POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC)

Protocol Number: **S1403**
Submitting Institution:

PATIENT INFORMATION
SWOG Patient ID # _____
JAX PDX # _____ (assigned by JAX)

SPECIMEN INFORMATION
Date collected: _____
Date Shipped: _____ (If different from date collected)

SPECIMEN TYPE
☐ **Biopsy –** Estimate of amount of tissue sent: # _____ Cores, _____ mm (L) x _____ mm (D)
☐ **Surgical resection** – Estimate amount of tissue ser # _____ Cores, _____ mm (L) x _____ mm (D)
☐ **Pleural Effusion –** Estimate volume of fluid sent: _____ ml

Is the submitted specimen free of necrotic tissue? ☐ **Yes** ☐ **No**
Is the submitted specimen free of excess blood? ☐ **Yes** ☐ **No**

Comments: _____

Prior sample on this patient submitted for PDX? ☐ **Yes** ☐ **No**
If yes, Prior patient study ID # _____

SITE PRINCIPAL INVESTIGATOR CONTACT INFORMATION
Name: _____
Primary Phone: _____
Email: _____

AUTHORIZATION
I certify that this specimen was collected with the patient's informed consent

X _____ Date _____

See page 2 for specimen collection and shipping instructions

PDX SPECIMEN COLLECTION AND SHIPPING INSTRUCTIONS

Contact Pathology prior to collection to coordinate and expedite sample processing.

The surgeon should obtain the maximum amount of tumor that is prudent at the time of biopsy or resection.

The specimen should be collected following Institutions Universal precautions SOPs for maintain tissue integrity and delivered immediately to Pathology. Please remind all personnel that are involved in processing the sample that it will be implanted in severely immune deficient mice, which is why we request that extra care be taken in sample collection to minimize the risk of transferring human bacteria to the mice.

Collection process for biopsy and surgical material

Materials needed:

Provided by JAX	Provided by the site
15ml tube containing transport media	Sterile forceps for transferring specimen to the tube containing transport media
50ml transport tube (no media)	Parafilm
Biohazard Specimen Bag 6” x 9”	Clean Gloves
Gelpacks	Alcohol or similar to clean gloves before handling the tissue
Insulated shipping container	
Prepaid shipping labels	

Using sterile forceps, transfer the tumor material collected at the time of biopsy or surgical resection to the 15 ml tube containing the transport media that is provided in the sample shipping kit. This transfer should occur as soon as possible, preferably within 30 minutes of tumor removal. The submitted tumor material should be free of necrotic or excessively bloody tissue.

Seal cap tightly with Parafilm and place in the larger 50 ml tube. This tube is provided for extra protection in shipping. Place the tube at 4 degrees until it is packed for shipping. This specimen for PDX development should NEVER be frozen.

Collection process for Pleural Effusions

Pleural fluid is collected and sent to cytology. Cytology staff will centrifuge ~40 - 50ml of the fluid. The remaining cells at the bottom of the tube (button) are then mixed with Transport Media and sent to JAX.

Packing and Shipping Instructions

JAX will provide shipping containers and labels. The sample will normally be shipped by Fed Ex unless it is collected too late in the day, in which case we will order a courier and have an electronic label sent to you. Contact cancer@jax.org as soon as the biopsy is scheduled to plan for the most expeditious shipping method.

Place the 50 ml tube containing the smaller tube with the tumor sample and transport media into the biohazard bag and seal (the biohazard bag is self-sealing). Place the bag in the insulated shipping container along with the gel packs that have been cooled to 4 ºC (0ºC~6 ºC); the gel packs should NEVER be frozen.

Ship the package according the previously agreed on method. Notify cancer@jax.org that the sample has been picked up. JAX will notify the study coordinator when the sample is received at its site.

V.2 103015

18.5 New York Heart Association Criteria

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

Informed Consent Model for S1403

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	58.4 (targeted above 55)
Flesch-Kincaid Grade Level	9.2 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as

well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Study Title for Study Participants: Testing the combination of afatinib and cetuximab compared to afatinib alone in newly diagnosed EGFR mutation positive, advanced stage non-small cell lung cancer

http://www.ClinicalTrials.gov: S1403, "A Randomized Phase II Trial of Afatinib Plus Cetuximab Versus Afatinib Alone in Treatment-Naive Patients with Advanced, EGFR Mutation Positive Non-Small Cell Lung Cancer (NSCLC) (BI 1200.124)"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

What is the usual approach to my advanced EGFR mutation positive non-small cell lung cancer?

You are being asked to take part in this study because you have newly diagnosed or recurrent non-small cell lung cancer which has spread to other parts of your body and has an EGFR (epidermal growth factor receptor) genetic mutation. An EGFR mutation is a change in a gene called EGFR. EGFR allows cells to grow and divide. People who are not in a study are usually treated with either the drug erlotinib or afatinib alone. Talk to your study doctor regarding your options.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

The purpose of this study is to compare any good and bad effects of using afatinib along with cetuximab to using afatinib alone. The addition of cetuximab to the usual afatinib could shrink your cancer, but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. T There will be about 212 people taking part in this study. The study will

be considered positive if the study approach delays disease progression. Afatinib is already FDA-approved for use in advanced non-small lung cancer and cetuximab is FDA-approved for treating other types of cancer, but using them together is considered investigational.

What are the study groups?

This study has two study groups.

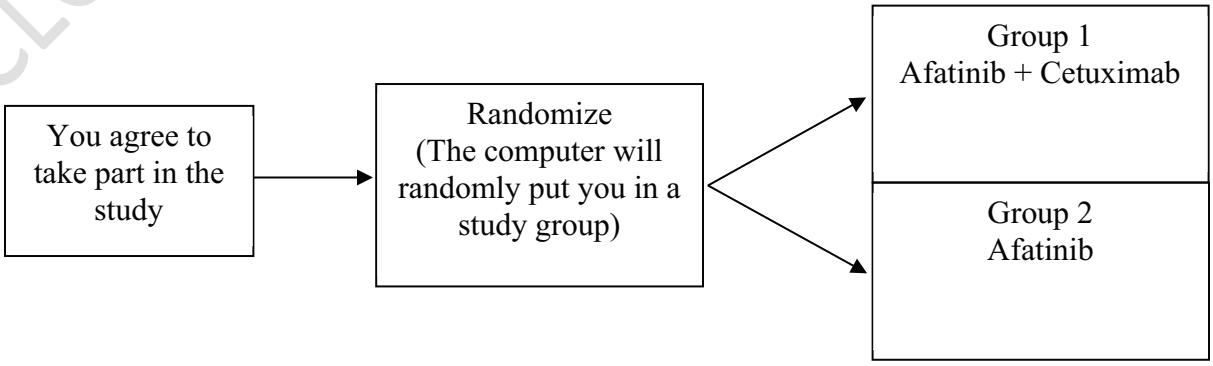
If you are in Group 1, you will receive the study drugs afatinib and cetuximab. The combination of the two drugs is considered investigational. Once every two weeks you will receive cetuximab which will be given into a vein. Before receiving cetuximab, you will receive diphenhydramine hydrochloride (Benadryl) to help prevent a hypersensitivity reaction. You will also take one afatinib tablet every day. Afatinib is to be taken by mouth on an empty stomach (at least one hour before eating or two hours after a meal). Every 28 days is considered a "cycle."

If you are in Group 2, you will receive afatinib alone. You will take one afatinib tablet every day. Afatinib is to be taken by mouth on an empty stomach (at least one hour before eating or two hours after a meal). Every 28 days is considered a "cycle."

To help keep track of the number of tablets you take and any side effects, you will need to keep a pill diary. The pill diary is called an Intake Calendar and you will need to bring it and the pill container with you for your follow-up visits. You should complete the pill diary daily.

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



How long will I be in this study?

You will receive study treatment (afatinib with cetuximab OR afatinib alone) until your disease gets worse or the side effects become too severe. If you stop taking the study treatment before your cancer gets worse, follow up exams will be every eight weeks until your cancer gets worse or three years from beginning the study (whichever comes first). After you are finished taking the study treatment, the study doctor will ask you to visit the office for follow up exams every six months for up to three years from beginning the study.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests that you will need to have if you take part in this study.

Before you begin the study:

You may need to have the following extra test to find out if you can be in the study:

- ECHO/MUGA scan and ECG to check for adequate cardiac function

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra tests and procedures.

- Researchers will use samples of your tissue and blood to learn what makes EGFR mutation positive tumors sensitive to and resistant to cetuximab and afatinib. The tissue and blood submissions are required because the research on them is an important part of the study.

  Sites that are not participating in the repeat biopsy study or the PDX study must include the following sentence: The tissue samples will be taken from a surgery or a biopsy that you have already had.

  Sites that are participating in the repeat biopsy study but not the PDX study must include the following paragraph: The tissue samples will be taken from a surgery or a biopsy that you have already had. If your disease shrinks with the study treatment but then begins to get bigger, another biopsy will be done at that time. A repeat biopsy is sometimes done as part of the usual medical care for people with your type of cancer, and in this case will also be used for the research purposes mentioned above.

  Sites that are participating in the repeat biopsy study and the PDX study must include the following paragraph: The tissue samples will be taken from a surgery or a biopsy that you have already had. If your disease shrinks with the study treatment but then begins to get bigger, another biopsy will be done at that time. A repeat biopsy is sometimes done

as part of the usual medical care for people with your type of cancer, and in this case will also be used for the research purposes mentioned above. As part of this research, a sample of your tissue will be inserted into a mouse to see how it grows and how it can be treated. In the future, a piece of the cancer growing in the mouse (not your tissue itself) may be sold to other researchers for other research. Future research could include developing new treatment or drugs. You will not receive any financial benefit from the research or products, including drugs, that might come from the use of your tissue.

The blood samples will be taken at three time points: before you begin the study treatment, before you begin Cycle 3 of study treatment, and if your disease gets worse. About two tablespoons of blood will be needed at each time.

Your privacy is very important and the researchers will make every effort to protect it. Results of tests done on your tissue and blood will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information.

The results of tests done on your tissue and blood are not part of normal clinical decision making, and will not be made available to you or your study doctor.

Neither you nor your health care plan/insurance carrier will be billed for the collection of your tissue and blood.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- **You may lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **You may be asked sensitive or private questions which you normally do not discuss**

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. There is also a risk that you could have side effects from the study drugs/study approach.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible side effect of Afatinib (all patients in Group 1 and Group 2)

Risk Profile for Afatinib (CAEPR Version 2.3, June 15, 2020)

COMMON, SOME MAY BE SERIOUS In 100 people receiving afatinib, more than 20 and up to 100 may have:
• **Diarrhea, nausea** • **Sores in the mouth which may cause difficulty swallowing** • **Tiredness** • **Infection** • **Rash**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving afatinib, from 4 to 20 may have:
• **Red, itchy eyes with increased watering** • **Redness and pain around lips** • **Constipation, heartburn, vomiting** • **Fever** • **Weight loss, loss of appetite** • **Dehydration** • **Pain** • **Changes in taste** • **Kidney damage which may require dialysis** • **Cough, shortness of breath, stuffy nose** • **Nose bleed** • **Dry skin** • **Itching, acne** • **Change in or loss of some or all of the fingernails or toenails**

RARE, AND SERIOUS In 100 people receiving afatinib, 3 or fewer may have:
• **A tear or hole in internal organs that may require surgery** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Change in heart function** • **Damage to the lungs which may cause shortness of breath** • **Redness, pain or peeling of palms and soles** • **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**

Possible Side Effects of Cetuximab (all patients in Group 1)
(Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS **In 100 people receiving Cetuximab, more than 20 and up to 100 may have:**
• **Change in nails** • **Swelling and redness of the area of radiation** • **Rash, itching, dry skin, acne** • **Dehydration, weight loss, loss of appetite** • **Sores in mouth which may cause difficulty swallowing** • **Constipation, diarrhea, vomiting, nausea** • **Difficulty sleeping** • **Headache, tiredness** • **Pain** • **Fever** • **Infection, especially when white blood cell count is low** • **Cough, shortness of breath**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cetuximab, from 4 to 20 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Confusion, depression, worry** • **Fainting** • **Severe blood infection** • **Blood clot which may cause swelling, pain, shortness of breath**

RARE, AND SERIOUS In 100 people receiving Cetuximab, 3 or fewer may have:
• **Scarring of the lungs** • **Kidney damage which may require dialysis** • **Heart stops beating**

Sites that are participating in the repeat biopsy study must include the following paragraph:

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection, collapsed lung requiring insertion of a tube in your chest, or hospitalization if tissue is taken from the primary lung tumor can occur. You will sign a separate consent form before the biopsy is taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study or for two weeks after your last afatinib dose and 2 months after your last cetuximab dose if in Group 1. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study drugs/study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. Participation is voluntary. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The afatinib and cetuximab will be supplied at no charge while you take part in this study whether you are in Group 1 or Group 2. The cost of getting the cetuximab ready and giving it to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that these drugs may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor, SWOG, and any drug company supporting the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- Qualified representative(s) of the Pharmaceutical Collaborator(s).
- Qualified representative(s) of the National Clinical Trial Network member with whom your institution is affiliated (ALLIANCE, ECOG-ACRIN, NRG, or SWOG).

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

OPTIONAL STUDIES SECTION

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, nor will you or your study doctor know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. Future contact

   Occasionally, researchers working with SWOG may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to future contact.

   I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

   Yes **No**

2. Biobanking for Possible Future Research

   Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

As mentioned in the main portion of the consent, samples of your tissue and blood will be used to study what makes EGFR mutation positive tumors sensitive to and resistant to cetuximab and afatinib. In this section of the consent, the researchers are asking your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and is supported by the National Cancer Institute.

What is involved?

If you agree to take part, here is what will happen next:

1) Your samples and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up.
2) Qualified researchers can submit a request to use the materials stored in the Biobank. A science committee at SWOG and/or the National Cancer Institute will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or

your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and *SWOG* staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

What if I have more questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

My samples and related information may be kept in a Biobank for use in future health research.

Yes **No**

THIS IS THE END OF THE SECTION ABOUT OPTIONAL STUDIES.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'.*

Participant's signature_____

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____