ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-A

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol A: Phase II Trial of Afatinib in Patients with Solid Tumors (Other Than Small Cell and Non-Small Cell Lung Cancer) or Lymphomas, That Have Activating Mutations of EGFR and Have Progressed After Standard Treatment

TREATMENT SUBPROTOCOL CHAIR: Scott Gettinger, MD
TRANSLATIONAL CHAIR: Karen Reckamp, MD

Version Date: May 16, 2018
NCI Update Date: August 12, 2015

NOTE: This subprotocol (EAY131-A) should be used in conjunction with the MATCH Master Protocol (EAY131).

Rev. Add13 **NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date.**

SUBPROTOCOL ACTIVATION DATE

August 12, 2015 (Incorporated in Addendum #1)
Update #2 – 8/15
Addendum #2 – 2/16
Addendum #3 – 5/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #8 – 3/17
Addendum #13

Agent	IND#	NSC#	Supply
Afatinib	IND Sponsor: DCTD, NCI IND #: 126200	750691	NCI Supplied

Table of Contents

TREATMENT SUBPROTOCOL CHAIR

Scott Gettinger, MD
333 Cedar Street
Medical Oncology FMP 127, PO Box 208032
New Haven, CT. 06520
Phone: 203-737-5312
Fax: 203-785-3788
E-mail: scott.gettinger@yale.edu

TRANSLATIONAL CHAIR

Karen Lynn Reckamp, MD
1500 East Duarte Road
Duarte, CA. 91010
Phone: 626-256-4673
Fax: 626-930-5461
E-mail: kreckamp@coh.org

Schema

Cycle = 28 days
Accrual Goal: 35

1. Introduction

Rev. Add13

1.1 Afatinib

Targeted treatments have proven to be clinically successful and represent the realization of precision medicine's potential. In non-small cell lung cancer (NSCLC), molecularly targeted treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have shown dramatic responses in patients with activating mutations (Lynch, Bell et al 2004; Paez, Jänne et al 2004; Mok, Wu et al 2009).

EGFR is a member of the human epidermal growth factor (HER) or ERBB family, a set of receptor tyrosine kinases that include EGFR (ERBB1), ERBB2, ERBB3, and ERBB4 (Pao and Chmielecki 2010). The receptors and their ligands regulate the proliferation of cancerous cells. *EGFR* mutations most frequently occur within exons 18-21, which constitute most of the tyrosine kinase binding domain of the receptor (Wu, Yu et al 2011). Exon 19 deletions (del19) and L858R within exon 21 are the two most common *EGFR* mutations in non-small cell lung cancer (NSCLC). These mutations alter the receptor's adenosine triphosphate (ATP) binding pocket by improving its affinity for ATP, resulting in constitutive activation (Herbst, Heymach et al 2008; Ohashi, Maruvka et al 2013). Reversible EGFR TKIs, erlotinib and gefitinib, preferentially bind to the receptor's ATP binding pocket, blocking ATP binding and the dimerization needed for receptor activation (Pao and Chmielecki 2010). In contrast, mutations such as exon 20 insertions and in-frame deletions or T790M alter the drug-receptor interaction and reduce ATP binding affinity to wild type receptor (Wu, Yu et al 2011).

Afatinib is a potent, irreversible, orally available ErbB family blocker that displays antitumor efficacy both in vitro and in vivo. Afatinib displays more selective antitumor activity than classical cytotoxic drugs that have an indiscriminate effect on all proliferating cells and has the potential to provide significant benefit to patients with advanced malignancies by inducing tumor responses or slowing of tumor progression and metastasis (Li, Ambrogio et al 2008; Yap, Vidal et al 2010). Afatinib is approved in the United States for the first-line treatment of patients with NSCLC whose tumors have non-resistant EGFR mutations as detected by an FDA-approved test.

1.2 Supporting Preliminary Data

Two multinational randomized Phase III studies of afatinib in the first line treatment of mutation positive stage IIIB/IV NSCLC patients have been performed: the LUX-Lung 3 (Sequist, Yang et al 2013) and LUX-Lung 6 (Wu, Zhou et al 2014) studies.

LUX-Lung 3 compared first line afatinib to cisplatin/pemetrexed and demonstrated afatinib's superiority to chemotherapy in *EGFR* mutation positive NSCLC patients (Sequist, Yang et al 2013). 345 patients with performance status 0-1 were randomized in a 2:1 ratio. In this trial patients treated with afatinib demonstrated significant and clinically meaningful improvements in progression free survival (PFS, median PFS afatinib vs. cisplatin/pemetrexed 11.1 vs. 6.9 months, hazard ratio 0.58; 95% CI. 0.43 to 0.78; P=.001) and Objective Response Rate (ORR, afatinib vs cisplatin /pemetrexed 56% vs. 23%; P= .001). There were significant delays in time to deterioration of the cancer-related

symptoms of cough (afatinib /cisplatin pemetrexed, Hazard Ratio, HR, 0.60; 95% CI, 0.41 to 0.87; P = .007) and dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; P =.01) in the afatinib treatment arm (Yang, Hirsch et al 2013). A pre-planned analysis of PFS in patients (n=308) with exon del 19 or L858R mutation was 13.6 months for afatinib and 6.9 months for chemotherapy (HR 0.47; 95% CI: 0.34 to 0.65; P=0.001). Higher response rates were observed in afatinib groups compared with chemotherapy 69% and 44%, respectively.

LUX-Lung 6 compared first line afatinib to up to six cycles of cisplatin/gemcitabine and 364 NSCLC patients were treated with 2:1 randomization (Wu, Zhou et al 2014). Patients treated with afatinib demonstrated significant improvements in progression free survival (median PFS afatinib vs. cisplatin/gemcitabine 11.0 months vs. 5.6 months, hazard ratio 0.28; 95% CI 0.20 to 0.39; P< 0.0001) and ORR (afatinib vs. cisplatin/gemcitabine 66.9% vs. 23.0 %, P < 0 .0001). This study also demonstrated significant delays in time to deterioration of the cancer-related symptoms of cough (afatinib vs. cisplatin/gemcitabine HR 0.45, 95% CI, 0.30 to 0.68; P = .0001) and dyspnea (HR 0.54; 95% CI, 0.40 to 0.73; P< 0.0001) in the afatinib treatment arm.

In a separate single arm study (LUX-Lung 2) in lung adenocarcinoma patients (stage IIIb with pleural effusion or stage IV) with EGFR mutations, 129 patients were treated in first-line or second-line with afatinib, 99 with a starting dose of 50 mg and 30 with a starting dose of 40 mg (Yang, Shih et al 2012). Seventy-nine (61%) of 129 patients had an objective response (two complete responses, 77 partial responses). 70 (66%) of the 106 patients with the two most common activating EGFR mutations (*deletion 19* or *L858R*) had an objective response, as did nine (39%) of 23 patients with less common mutations.

For NSCLC patients previously treated with a reversible EGFR TKI and clinically enriched for EGFR mutations, treatment with afatinib plus best supportive care resulted in a significant improvement in median PFS over patients treated with a placebo plus best supportive care in LUX-Lung 1 (Miller, Hirsch et al 2012). This improvement in PFS was accompanied by significant and meaningful improvements in cough, dyspnea, and pain, compared to the placebo group. Treatment with afatinib was also found to significantly delay the time to deterioration for Global health status/Quality of Life (QoL).

A subsequent and larger study (LUX-Lung 5) enrolling a similar population of NSCLC patients resulted in a very similar median PFS as in LUX-Lung 1. In these studies, the PFS benefit of afatinib was consistent across all pre-planned subgroups with at least 50 patients, including gender, age, race, baseline Eastern Cooperative Oncology Group (ECOG) performance status, type of prior EGFR TKI, baseline tumor size, and lines of prior chemotherapy. In both of these studies (LUX-Lung 2 and 5) treatment with afatinib had the greatest PFS benefit for those patients who belonged to a subgroup highly clinically enriched for EGFR mutations or who were positive for EGFR mutations by testing of tumor tissue.

The significant benefit of afatinib in NSCLCs that have driver activating EGFR mutations argues for the evaluation of the effect of afatinib in other tumors with similar EGFR, and likely driver, mutations. The frequency of activating EGFR mutations is uncommon outside NSCLC, in tumors where EGFR mutations have been evaluated see Table below. The genomic alterations associated with

deletions in exon 19 and substitutions in exon 21 (in addition to other variants) are highly sensitive to EGFR TKI inhibition (Lynch, Bell et al 2004; Shan, Eastwood et al 2012). Therefore, it is reasonable to assess the objective response and progression free survival of patients with tumors other than NSCLC.

Tumor site	EGFR alteration (%)
Breast	0
CNS	3
Colon	0
Head and neck	2
Prostate	4
Urinary tract	1

2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

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 four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: All patients must have signed the relevant treatment consent form

2.1 Eligibility Criteria

Rev. 2/16

_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

Rev. 2/16
Rev. Add13

_____ 2.1.2 Patient's tumor must have either of the below, or another aberration, as determined via the MATCH Master Protocol and according to Appendix III:

_____2.1.2.1 Activating mutations of EGFR (del 19, L858R).

OR

_____2.1.2.2 Any malignancy harboring any of the following mutations: EGFR G719A, G719C, G719D, G719S EGFR L861Q, EGFR S768I

_____2.1.2.3 Tumors with an exon 20 insertion alone without the above mutations will be excluded.

See Appendix III for information on the targeted mutations and the corresponding Levels of Evidence (LOE).

_____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).

Date of ECG: _____

Rev.2/16 _____ 2.1.4 Patients with known left ventricular dysfunction must have ECHO or a nuclear study (MUGA or First Pass) within 4 weeks prior to registration to treatment and must not have left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN). If the LLN is not defined at a site, the LVEF must be > 50% for the patient to be eligible.

Date of ECHO/nuclear study: _____

NOTE: Pre-treatment LVEF determination in patients without known left ventricular dysfunction is NOT otherwise required.

_____ 2.1.5 Patients must not have known hypersensitivity to Afatinib or compounds of similar chemical or biologic composition.

_____ 2.1.6 Patients must have ≤ Grade 1 renal function as defined below:

Creatinine ≤ 1.5 x normal institutional limits

OR

Measured Creatinine clearance ≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal or as calculated by the Cockcroft-Gault Equation.

Creatinine clearance: _____

The above renal eligibility criteria should be strictly followed and will override the MATCH Master Protocol requirements.

Rev.12/16 _____ 2.1.7 Patients must not have had prior treatment with an EGFR TKI (e.g. Afatinib, Erlotinib, Gefitinib, Neratinib, Dacomitinib, AZD9291, Cabertinib, CO-1686).

_____2.1.8 Patients with non-small cell lung cancer and small cell lung cancer will be excluded.

_____ 2.1.9 Patients with a history of interstitial lung disease will be excluded.

_____2.1.10 Patients must have ≤ Grade 1 diarrhea at baseline.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3. Afatinib Treatment Plan

Rev. 12/16

3.1 Administration Schedule

Afatinib 40 mg PO QD, repeat cycles every 28 days until progression of disease, unacceptable toxicities or withdrawal of consent.

NOTE: Afatinib tablets are taken once daily. Afatinib tablets should not be chewed nor crushed.

NOTE: Do not take Afatinib with food. Afatinib should be taken at least one hour before food intake, or at least two hours after food intake.

Missed doses should not be administered if within 12 hours of the next scheduled dose. If vomiting occurs after taking a dose of afatinib, the patient should not take an additional dose as a replacement.

3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

3.2.1 Additional adverse event reporting instructions, requirements and exceptions for EAY131 – Subprotocol A

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

EAY131 – Subprotocol A specific expedited reporting requirements:

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on Afatinib, or within 28 days of the subject's last dose of Afatinib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131 – Subprotocol A specific expedited reporting exceptions:

For Subprotocol A, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirement of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

3.2.2 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. 3/17

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Afatinib (NSC 750691)

The Comprehensive Adverse Event 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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). 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.

NOTE: If an AE meets the reporting requirement of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 2.1, October 10, 2016[1]

Adverse Events with Possible Relationship to Afatinib (CTCAE 4.0 Term) [n= 2596]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
EYE DISORDERS			
	Eye disorders - Other (eye disorder)[2]		
GASTROINTESTINAL DISORDERS			
	Cheilitis		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Mucositis oral[3]			***Mucositis oral[3] (Gr 2)***
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
INFECTIONS AND INFESTATIONS			
Infection[4]			***Infection[4] (Gr 2)***

Adverse Events with Possible Relationship to Afatinib (CTCAE 4.0 Term) [n= 2596]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Creatinine increased[5]		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypokalemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Musculoskeletal and connective tissue disorder - Other (muscle spasm/ twitching)		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
RENAL AND URINARY DISORDERS			
	Renal and urinary disorders - Other (renal impairment)[5]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 2)***
	Nasal congestion		
		Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[6]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Pruritus		
	Rash acneiform		
	Skin and subcutaneous tissue disorders - Other (nail effect)[7]		***Skin and subcutaneous tissue disorders - Other (nail effect)[7] (Gr 2)***

Adverse Events with Possible Relationship to Afatinib (CTCAE 4.0 Term) [n= 2596]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Skin and subcutaneous tissue disorders - Other (rash)[8]			***Skin and subcutaneous tissue disorders - Other (rash)[8] (Gr 2)***
		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]Mucositis oral (stomatitis) may include stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, and mucosal ulceration.

[4]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[5]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.

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

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

[8]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

HEPATOBILIARY DISORDERS - Hepatic failure

IMMUNE SYSTEM DISORDERS - Allergic reaction

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Ejection fraction decreased; 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) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (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 - Female genital tract fistula; Pelvic pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pleural effusion; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal dryness); Respiratory, thoracic and mediastinal disorders - Other (nasal inflammation); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal discomfort)

SKIN AND CUTANEOUS 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.

Rev.2/16

3.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Afatinib will be administered at the recommended dose of 40 mg orally once daily starting on the first day of administration and continue until disease progression or unacceptable toxicity. We chose the 40 mg daily dose since the Css still remains adequate at this dose. High Rates of dose modification were seen in previous studies with 50 mg daily dosing.

Afatinib will not be held for hematologic toxicity, unless it is determined to be a drug-related grade 3 or 4 hematologic event.

Treatment may be delayed by 2 weeks due to toxicity. If treatment is delayed beyond 2 weeks the subject will come off study for unacceptable toxicity. **Discontinuation of afatinib for any reason for more than 2 weeks will result in removal of the patient from this subprotocol.**

The afatinib dose may be adjusted according to individual patient tolerance as outlined below.

Table 1. Dose Levels for Afatinib

Dose Level	Daily Dose/ Route	Dispensed As	Schedule.
Starting dose level: 0	40 mg, PO	1 × 40-mg tablet	Daily during 4- week cycle
–1	30 mg, PO	1 × 30 mg tablet	Daily during 4- week cycle
–2	20 mg, PO	1 × 20-mg tablet	Daily during 4- week cycle

3.4.1 Treatment compliance

Records of study medication usage and doses administered will be kept during the accountability will be noted. Patients will be asked to return all unused medication.

3.4.2 Toxicity monitoring & dose modification

Patients will have clinical and laboratory assessment while on study as per the Study Calendar. No dose escalations of afatinib will be permitted.

In the event of any CTC, version 4.0 drug-related grade 3 or 4 non-hematologic adverse event(s), drug should be held until the toxicity resolves to ≤ grade 1 and then the drug should be restarted at a one dose-level reduction with the exception noted in table 2. In addition, no dose modifications will be needed for low electrolytes (Na, K, Phos, Mg) unless the grade 3 or 4 adverse event were to last > 48

hours despite optimal electrolyte repletion. Please see supportive care guidelines for nausea, vomiting, diarrhea, fatigue, and rash.

Patients should be carefully monitored for clinical signs and symptoms of CHF while receiving afatinib. In the presence of clinical manifestations of CHF, discontinuation of afatinib and assessment of LVEF is recommended.

In the event of any CTC, version 4.0 drug-related grade 3 or 4 hematologic adverse event(s), the drug should be held until the toxicity resolves to ≤ grade 1 and then the drug should be restarted at a one dose-level reduction.

3.4.3 Dose reduction for afatinib

Intra-patient dose reduction by 1, and if needed 2, dose-levels will be allowed depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal from study treatment have not been met. Intrapatient dose re-escalation is not allowed.

All intra-patient dose reductions are relative to the lowest dose level of the current cycle.

Recovery to acceptable levels of toxicity must occur within 2 weeks to allow continuation in the study.

No more than 2 dose reductions are permitted for any patient. If further dose reduction is required, the patient must be removed from the study.

The following table describes the recommended dose modifications for study treatment associated toxicity:

Table 2. Dose Modification for Afatinib				
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Non-hematologic Toxicity (except specific toxicities mentioned below)[a,b,c]	**Continue at the same dose level.**	**Continue at the same dose level.**	**Withhold dose until toxicity is grade ≤ 1 or has returned to baseline. Then reduce the dose by 1 level and resume treatment.**	**Withhold dose until toxicity is grade ≤ 1 or has returned to baseline. Then reduce the dose by 1 level or discontinue treatment (discretion of the investigator).**
Cardiac Toxicity	**Continue at the same dose level.**	**Continue at the same dose level except for asymptomatic decrease of LVEF by an absolute value of 20% (or more) and to < institutional LLN. Withhold dose until toxicity is grade ≤ 1. Then reduce dose by 1 level and resume treatment.**	**Discontinue study treatment.**	**Discontinue study treatment.**
Renal Toxicity	**Continue at the same dose level.**	**Withhold dose until toxicity is grade ≤ 1. Then reduce dose by 1 level and resume treatment.**	**Withhold dose until toxicity is grade ≤ 1. Then reduce dose by 1 level and resume treatment.**	**Withhold dose until toxicity is grade ≤ 1. Then reduce dose by 1 level and resume treatment or discontinue treatment (discretion of the investigator).**
Diarrhea	**Continue at the same dose level.[b]**	**Continue at the same dose level unless diarrhea persists for 2 or more days despite adequate anti-diarrheal medication or hydration. Withhold dose until toxicity is grade ≤ 1. Then reduce dose by 1 level and resume treatment.**	**Withhold dose until toxicity is grade ≤ 1. Then reduce dose by 1 level and resume treatment.**	**Withhold dose until toxicity is grade ≤ 1 Then reduce dose by 1 level and resume treatment.**
Rash (Papulopustular, pustular, acneiform, maculo-papular)[d]	**Continue at the same dose level.**	**Continue at the same dose level unless rash persists and is intolerable or worsens over > 7days. If this occurs: Withhold dose until toxicity is grade ≤ 1. Then reduce dose by 1 level and resume treatment.**	**Withhold dose until toxicity is grade ≤ 1. Then reduce dose by 1 level and resume treatment.**	**Discontinue study treatment**
Drug-induced hepatic impairment	**Continue at the same dose level.**	**Continue at the same dose level.**	**Withhold dose until toxicity is grade ≤ 1 or has returned to baseline. Then reduce the dose by 1 level and resume treatment.**	**Discontinue study treatment**

Ulcerative keratitis	**Continue at the same dose level.**	**Continue at the same dose level.**	**Withhold dose until toxicity is grade ≤ 1 or has returned to baseline. Then reduce the dose by 1 level and resume treatment.**	**Discontinue study treatment**
Interstitial lung disease	**If a patient develops respiratory problems consistent with possible interstitial lung disease (ILD), afatinib is to be withheld pending a diagnostic evaluation. Afatinib will be discontinued if a diagnosis of ILD is confirmed.**			

a. No dose modifications will be needed for low electrolytes (Na, K, Phos, Mg) unless the grade 3 or 4 adverse event were to last > 48 hours despite optimal electrolyte repletion

b. See supportive care for diarrhea in Section 3.5.1

c. Nausea and vomiting should be graded after maximal medical management

d. See supportive care for rash in Section 3.5.1

Potential Drug Interactions: Afatinib is a substrate of P-glycoprotein (P-gp). Concomitant use of strong P-gp inhibitors and inducers should be used with caution. Strong P-gp inhibitors (e.g., ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) may increase exposure to afatinib. Strong P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's Wort) may decrease exposure to afatinib. If strong P-gp inhibitors need to be concomitantly administered with afatinib, they should be administered simultaneously with or after afatinib administration.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as Facts and Comparisons or Lexicomp; medical reference texts such as the Physicians' Desk Reference may also provide this information. The Principal Investigator should be alerted if the subject is taking any agents that are strong P-gp inhibitors or inducers.

3.5 Supportive Care

3.5.1

All supportive measures consistent with optimal patient care will be given throughout the study.

After a treatment pause the dose of afatinib should be reduced according to the dose reduction scheme in Table 1. The occurrence of nausea and/or vomiting will be recorded in the AE section of the eCRF.

Management of Diarrhea

Close monitoring and proactive management of diarrhea is essential for successful treatment of patients with afatinib. Early and appropriate intervention can prevent the development of more severe diarrhea. In most cases, loperamide (Imodium) controls diarrhea caused by afatinib.

The recommendations for management are as follows:

If any diarrhea is experienced (CTCAE Grade 1), two 2 mg loperamide tablets (total dose 4 mg) should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 8 tablets (16 mg).Other anti-diarrheal medications that could be uses include: Lomotil (5 mg, four times a day), or tincture of opium (15-20 drops orally every 4 hours) or octreotide (150 to 300 micrograms SQ twice a day).

Rev.2/16

Oral hydration is important regardless of severity of diarrhea; appropriate rehydration (1.5L/m^2/day plus equivalent of actual fluid loss) and electrolyte replacement should be recommended in the event of CTCAE Grade 2 and Grade 3 diarrhea.

Management of Rash

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 reduce the rash. The recommendations for management are as follows:

General/Prevention: strict sun protection; use of a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide; use of a thick, alcohol-free emollient cream.

CTCAE Grade 1 rash: mild rash may not need treatment. However, if treatment is considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel/lotion can be used.

CTCAE Grade 2 rash: relief from major symptoms caused by CTCAE Grade 2 skin related adverse events should be achieved by a combination of local and systemic therapies including:

1. Systemic antibiotics (e.g. doxycycline or minocycline etc.).
2. Topical treatment (e.g. hydrocortisone 2.5% cream, clindamycin 1% gel/lotion, pimecrolimus 1% cream). And / or 1) Antihistamines (e.g. diphenhydramine, etc.)
3. Oral corticosteroid (low dose and short term i.e., < 10 days treatment) may be added at investigator's discretion.

Systemic and topical treatment should be initiated at the start of CTCAE Grade 2 rash and continued until improvement or resolution to CTCAE Grade ≤ 1. If grade 2 rash persists for ≥ 7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment for up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 2.

Management of Fatigue

For intolerable fatigue (grade ≥ 3), the next cycle of treatment may be delayed by up to two weeks.

Management of Interstitial Lung Disease

Although quite rare, interstitial lung disease (ILD) is a class effect of EGFR TKIs and can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. Chest CT should be obtained to look for interstitial fibrotic changes if ILD is suspected. In the event that ILD is suspected, drug treatment should be discontinued and the patient should receive appropriate medical management and supportive care. Although there is no established treatment, systemic corticosteroids are often administered. Afatinib should not be restarted in those patients suspected of having drug-related ILD and the subject should be removed from the study.

3.6 Duration of Agent-specific treatment

In the absence of treatment delays due to adverse event(s); treatment may continue until one of the following criteria applies:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be

discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.

- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

3.7 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

Rev.12/16
Rev.3/17

4. Study Parameters

Rev.2/16

4.1 Therapeutic Parameters for Afatinib Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving afatinib treatment.

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

Test/Assessment	Prior to Registration to Treatment	Treatment			End of Treatment	Follow Up[F]
		Cycle 1, day 8 and day 15[G]	Every Cycle, prior to treatment	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X		X[J]			X
Performance status	X	X	X[J]			X
CBC w/diff, plts[B]	X		X[J]			X
Serum chemistry[B]	X		X[J]			X
Radiologic evaluation[D]	X			X[D]		X[F]
β-HCG[C]	X					
Toxicity Assessment[G]		X	X		X	X[F]
Pill Count/Diary[H]			X		X	
ECG[K]	X		X[I]			
Echocardiogram or Nuclear Study[K]	X[I]		X[I]			X[I]
Tumor biopsy and blood sample for MATCH Master Protocol[E]				X	X	

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

Rev.2/16

B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

Rev.2/16

C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.

Rev.2/16

D. Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks

before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

Rev. Add13 E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

Rev.2/16 F. Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

G. Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

H. The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but is required every subsequent cycle.

I. As clinically indicated

J. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital signs; Performance Status; CBC w/diff plts; Serum chemistry; Concomitant Medications.

Rev.2/16 K. Within 8 weeks of treatment assignment (or within 4 weeks prior to registration to treatment for ECHO/nuclear study if clinically indicated, per Section 2.1.4)

Rev. Add13 **5. Drug Formulation and Procurement**

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by the eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam) and the maintenance of an “active” account status, a “current” password, and an active person registration status.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Rev. 12/16 **Drug Accountability:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

Rev.3/17 **Investigator Brochure Availability:** The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov

5.1 Afatinib (NSC 750691)

5.1.1 Other Names

BIBW 2992; afatinib dimaleate, Gilotrif®

5.1.2 Classification

Tyrosine Kinase Inhibitor

5.1.3 Mode of Action

Afatinib is a potent and selective irreversible ErbB family blocker, binding to kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4).

5.1.4 Storage and Stability

Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Stability: Commercial packaged bottles are labeled with the expiration date. Dispense medication in the original container to protect from exposure to high humidity and light.

5.1.5 Dose Specifics

Afatinib 40 mg PO QD, repeat cycles every 28 days. Afatinib tablets should not be chewed nor crushed.

5.1.6 Preparation

Afatinib is supplied by Boehringer Ingelheim and distributed by CTEP, DCTD, NCI as afatinib dimaleate film-coated tablets containing 40 mg, 30 mg or 20 mg of afatinib in polypropylene bottles with desiccants and containing 30 tablets each. Tablet descriptions are as follows:

40 mg: light blue, film-coated, round, biconvex, bevel-edged tablets, 10 mm diameter, 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, 9 mm diameter, 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, 8 mm diameter, debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.

Inactive ingredients:

Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate.

Coating: hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

5.1.7 Route of Administration

Oral. Administer afatinib on an empty stomach; at least 1 hour before or 2 hours after a meal. Missed doses should not be administered if within 12 hours of the next scheduled dose.

5.1.8 Incompatibilities

Afatinib is a substrate of P-glycoprotein (P-gp). Concomitant use of strong P-gp inhibitors and inducers should be used with caution. Strong P-gp inhibitors (e.g., ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) may increase exposure to afatinib. Strong P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's Wort) may decrease exposure to afatinib. If strong P-gp inhibitors need to be concomitantly administered with afatinib, they should be administered simultaneously with or after afatinib administration.

5.1.9 Side Effects

See Section 3.3 for side effects.

6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

7. References

Herbst RS, Heymach J V, Lippman SM. Lung cancer. *N Engl J Med*. 2008;359:1367-80.

Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene*. 2008;27:4702-4711.

Lynch TJT, Bell DDW, Sordella R, et al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib. *N Engl J Med*. 2004;350:2129-2139.

Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol*. 2012;13:528-538.

Mok TTS, Wu Y-LY, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947-957.

Ohashi K, Maruvka YE, Michor F, Pao W. Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. *J Clin Oncol*. 2013;31:1070-80.

Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497-500.

Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. *Nat Rev Cancer*. 2010;10:760-74.

Schuler MH, Planchard D, Yang JCH, et al. Interim analysis of afatinib monotherapy in patients with metastatic NSCLC progressing after chemotherapy and erlotinib/gefitinib (E/G) in a trial of afatinib plus paclitaxel versus investigator's choice chemotherapy following progression on afatinib monotherapy. *J Clin Oncol*. 2012; 30: (suppl; abstr 7557).

Sequist L V, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327-34.

Shan Y, Eastwood MP, Zhang X, et al. Oncogenic mutations counteract intrinsic disorder in the EGFR kinase and promote receptor dimerization. Cell 2012; 149: 860-70.

Wu J-Y, Yu C-J, Chang Y-C, Yang C-H, Shih J-Y, Yang P-C. Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer. *Clin Cancer Res*. 2011;17:3812-21.

Wu Y-L, Zhou C, Hu C-P, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:213-22.

Yang JC-H, Shih J-Y, Su W-C, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. *Lancet Oncol*. 2012;13:539-48.

Yang JC-H, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3342-50.

Yap TA, Vidal L, Adam J, et al. Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors. *J Clin Oncol*. 2010;28:3965-72.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol A: Afatinib

Appendix I

Rev.12/16

Patient Pill Calendar

Rev.3/17

Storage: Store at Room Temperature

Pill Calendar Directions

1. Take your scheduled dose of each tablet.
2. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
3. Take afatinib on an empty stomach at least 1 hour before or 2 hours after a meal.
4. Afatinib tablets are taken once daily. Afatinib tablets should not be chewed nor crushed.
5. Missed doses should not be administered if within 12 hours of the next scheduled dose.
6. Do not take an additional dose as a replacement if vomiting were to occur after taking a dose of Afatinib.
7. Limit time in the sun, sun exposure can cause rash and severe sunburn. Apply sunscreen, wear hat and protective clothing for any sun exposure.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each tablet. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

Afatinib

DAY	Date			Time tablets taken	Dose of tablets taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year			
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol A: Afatinib

Appendix II

Patient Drug Information Handout and Wallet Card

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The patient _____ is enrolled on a clinical trial using the experimental agent Afatinib. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

Afatinib interacts with other drugs. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Afatinib interacts with other drugs that effect P-glycoprotein, a protein on the surface of cells in our body that helps move drugs and other substances in and out of cells.

- Afatinib must be used very carefully with other medicines that increase the activity of P-glycoprotein (inducers) or decrease the activity of P-glycoprotein (inhibitors).
    - Substances that increase the activity of P-glycoprotein ("inducers") could reduce the effectiveness of afatinib, while substances that decrease the activity of P-glycoprotein ("inhibitors") could result in high levels of afatinib, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors P-glycoprotein."
- Your prescribers should consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you.

Your study doctor's name is:

_____

and he or she can be contacted at:

_____.

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent **Afatinib**. This clinical trial is sponsored by the NCI. **Afatinib** interacts with drugs that effect P-glycoprotein. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Afatinib** interacts with drugs that effect P-glycoprotein and must be used very carefully with other medicines that interact with P-glycoprotein. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors of P-glycoprotein." ➢ Before prescribing new medicines, your regular prescribers should go to medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol A: Afatinib

Rev.2/16
Rev. Add13

Appendix III

Actionable Mutations of Interest (aMOIs)

A. Inclusion Variants:

NOTE: A function has been implemented in MATCHBOX to identify any novel in-frame deletions in exon 19 of the EGFR gene at Level of Evidence code 1. This function also includes any activating mutation in the EGFR gene with Level of Evidence code 3 or higher not listed in the table below. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
EGFR	COSM6224	SNV	1	p.L858R
EGFR	COSM6252	SNV	2	p.G719S
EGFR	COSM6253	SNV	2	p.G719C
EGFR	COSM18425	SNV	2	p.G719D
EGFR	COSM6239	SNV	2	p.G719A
EGFR	COSM6213	SNV	2	p.L861Q
EGFR	COSM18441	MNV	2	p.G719C
EGFR	COSM6241	SNV	2	p.S768I
EGFR	COSM26038	Large Indel	1	p.K745_E749del
EGFR	COSM1190791	Large Indel	1	p.K745_A750delinsT
EGFR	COSM28517	Large Indel	1	p.E754_E757del
EGFR	COSM18420	Indel	1	p.E754del
EGFR	COSM24869	Large Indel	1	p.E754_T759del
EGFR	COSM6223	Large Indel	1	p.E754_A758del
EGFR	COSM13551	Large Indel	1	p.E746_T751delinsI
EGFR	COSM13550	Large Indel	1	p.E746_A750delinsIP
EGFR	COSM13552	Large Indel	1	p.E746_T751delinsIP
EGFR	COSM13549	Large Indel	1	p.E746_T751delinsA
EGFR	COSM133189	Large Indel	1	p.E746_S752del
EGFR	COSM6225	Large Indel	1	p.E746_A750del
EGFR	COSM6218	Large Indel	1	p.E746_R748del
EGFR	COSM12728	Large Indel	1	p.E746_T751del
EGFR	COSM26680	Large Indel	1	p.E746_T751delinsI
EGFR	COSM51526	Large Indel	1	p.E746_T751delinsIP

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
EGFR	COSM24970	Large Indel	1	p.L755_K762del
EGFR	COSM12678	Large Indel	1	p.E746_T751delinsA
EGFR	COSM12367	Large Indel	1	p.E746_S752delinsA
EGFR	COSM12386	Large Indel	1	p.E746_T751delinsV
EGFR	COSM133192	Large Indel	1	p.E746_T751delinsV
EGFR	COSM18426	Large Indel	1	p.E746_S752delinsV
EGFR	COSM18427	Large Indel	1	p.E746_P753delinsVS
EGFR	COSM133193	Large Indel	1	p.E746_T751delinsV
EGFR	COSM674057	Large Indel	1	p.E746_S752delinsV
EGFR	COSM53205	Large Indel	1	p.E746_T751delinsVa
EGFR	COSM12384	Large Indel	1	p.E746_S752delinsV
EGFR	COSM12416	Large Indel	1	p.E746_T751delinsVa
EGFR	COSM255211	Large Indel	1	p.E746_P753delinsG
EGFR	COSM6254	Large Indel	1	p.E746_T751delinsG
EGFR	COSM6220	Large Indel	1	p.E746_S752delinsG
EGFR	COSM12419	Large Indel	1	p.L747_T751delinsQ
EGFR	COSM12422	Large Indel	1	p.L747_A750delinsP
EGFR	COSM22944	Large Indel	1	p.L747_T751delinsP
EGFR	COSM6255	Large Indel	1	p.L747_S752del
EGFR	COSM51527	Large Indel	1	p.L747_T751delinsQ
EGFR	COSM133195	Large Indel	1	p.L747_A750delinsP
EGFR	COSM12387	Large Indel	1	p.L747_P753delinsQ
EGFR	COSM12420	Large Indel	1	p.L747_T751delinsQ
EGFR	COSM12382	Large Indel	1	p.L747_A750delinsP
EGFR	COSM12383	Large Indel	1	p.L747_T751delinsP
EGFR	COSM12370	Large Indel	1	p.L747_P753delinsS
EGFR	COSM6210	Large Indel	1	p.L747_T751delinsS
EGFR	COSM23634	Large Indel	1	p.A750_E758delinsG
EGFR	COSM1667024	Large Indel	1	p.T751_I759delinsN
EGFR	COSM96856	Large Indel	1	p.T751_I759delinsN
EGFR	COSM24270	Large Indel	1	p.T751_I759delinsN
EGFR	COSM13556	Large Indel	1	p.T751_I759delinsN
EGFR	COSM6256	Large Indel	1	p.S752_I759del

B. Exclusion Variants:

A function has been implemented in MATCHBOX to identify any novel in-frame insertions in exon 20 of the EGFR gene at Level of Evidence code 2.

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
EGFR	COSM6240	SNV	2	p.T790M