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

Operations Office

July 10, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #21 to EAY131-B, *Phase II Study of Afatinib in Patients with Tumors with HER2 Activating Mutations.*

Please replace your current copy of the protocol and Informed Consent document (if ICD changed) with this (these) updated version(s). We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB which is the sole IRB of record for this study.

Implementation of this addendum must occur on the activation date. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.]

This addendum is in response to Dr. Jeffrey Moscow's June 19, 2019 Request for Rapid Amendment for Afatinib.

The following revisions to EAY131-B protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version date.
2.	3.3	Updated the Afatinib CAEPR list with version 2.2, April 24, 2019.

The following revisions to EAY131-B Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.
2.	What possible risks can I expect from taking part in this study?	Updated the Afatinibpossible risks risk list with version 2.2 April 24, 2019.

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

If you have any questions regarding this addendum, please contact aagu@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EAY131-B so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Enclosure

CC:
Phillpe Bedard MD
Kari B. Wisinki, MD
Eddy Yang, MD
Alice Chen, MD
Keith Thomas Flaherty, MD
Lyndsay N. Harris. MD
Peter O'Dwyer, MD
Mickey Williams, PhD
James V. Tricoli, PhD
Stanley Hamilton, MD
Lisa McShane, PhD
Larry Rubinstein, PhD
Robert Gray, PhD
Shuli Li, PhD
Lalitha Shankar, MD
Susanna Lee, MD, PhD
Constantine Gastonis, PhD
Paolo Caimi, MD
Shaji Kumar, MD
Carlos Arteaga, MD
Edith Mitchell, MD
John J. Wright, MD, PhD
Bruce Giantonio, MD
Donna Marinucci
Kerry Higgins
Gayle Ipock
Jean MacDonald
Carol Chami, R.N.
Juanita Andrews
Melinda Flood
Kelly Redmond
Becky Fillingham
Kevin Pollard
Abuchi Agu
Elanna Radomyshelsky
Camilla Abreu
Michael T. Balco
Lauren Lambert
Cayden Maican
Margaret Cavenagh
Ben Kim
Alexandra Sachs

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

EAY131-B

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol B: Phase II Study of Afatinib in Patients with Tumors with HER2 Activating Mutations

Rev. 5/16

AFATINIB TREATMENT SUBPROTOCOL CHAIR: Philippe Bedard, MD
AFATINIB TREATMENT SUBPROTOCOL CO-CHAIR: Kari B. Wisinski, MD
AFATINIB TRANSLATIONAL CHAIR: Eddy Yang, MD, PhD

Version Date: July 10, 2019
NCI Update Date: August 12, 2015

NOTE: This subprotocol (EAY131-B) 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
Addendum #21

Agent	IND#	NSC#	Supply
Afatinib			NCI Supplied

Table of Contents

Molecular Analysis for Therapy Choice (MATCH) i
MATCH Treatment Subprotocol B: Phase II Study of Afatinib in Patients with Tumors with HER2 Activating Mutations 1
Table of Contents 2
Schema 4
1. Introduction 5
1.1 HER2 mutations are responsive to Afatinib dimaleate (BIBW 2992, Gilotrif®) 5
2. Selection of Patients 17
2.1 Eligibility Criteria 17
3. Afatinib Treatment Plan 19
3.1 Administration Schedule 19
3.2 Adverse Event Reporting Requirements 19
3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Afatinib (BIBW 2992, NSC 750691) 22
3.4 Dose Modifications 26
3.5 Supportive Care 30
3.6 Duration of Agent-specific treatment 31
3.7 Duration of Follow-Up 31
4. Study Parameters 32
4.1 Therapeutic Parameters for Afatinib Treatment 32
5. Drug Formulation and Procurement 34
5.1 Afatinib (NSC 750691) 35
6. Translational Studies 37
7. References 37
Appendix I Patient Pill Calendar 41
Appendix II Patient Drug Information Handout and Wallet Card 43
Appendix III Actionable Mutations of Interest (aMOIs) 45

Rev. 5/16
Rev. 3/17
Rev. Add13

TREATMENT SUBPROTOCOL CHAIR

Philippe Bedard, MD
University of Toronto
Princess Margaret Cancer Centre
OPG Building, 700 University Avenue 7th floor
7-723
Toronto, ON, Canada, M5G 1Z9
Phone: (416) 946-4534
Fax: (416) 946-6546
Email: Philippe.Bedard@uhn.ca

TREATMENT SUBPROTOCOL CO-CHAIR

Kari B. Wisinski, MD
Univ. of Wisconsin Carbone Cancer Center
1111 Highland Ave, WIMR 6033
Madison, WI 53705-2275
Phone: 608- 262-2876
Fax: 608- 265-6905
Email: kbwisinski@medicine.wisc.edu

TRANSLATIONAL CHAIR

Eddy S. Yang, MD, PhD
University of Alabama-Birmingham
176F HSROC Rm 2232N
1700 6th Avenue South
Birmingham AL 35249-6832
Phone: 205-934-2762
Fax: 205-975-0784
Email: eyang@uab.edu

Rev. 3/17

Schema

Cycle = 28 days
Accrual Goal: 70

1. Introduction

Rev. 3/17

1.1 HER2 mutations are responsive to Afatinib dimaleate (BIBW 2992, Gilotrif®)

The human epidermal growth factor receptor (HER) family pathway plays a critical role in multiple cellular functions. There are four members in this family: HER1 (epidermal growth factor receptor [EGFR] or ErbB1), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). Activation of the pathway via homo- or heterodimerization of these receptors can lead to cell proliferation, differentiation and survival.[1] Agents targeting EGFR and HER2 have demonstrated activity in selected malignancies with HER2 overexpression/amplification or EGFR mutations.

The human epidermal growth factor receptor-2 (ErbB2, HER2) is a transmembrane tyrosine kinase receptor which regulates cell growth and survival, as well as adhesion, migration, differentiation, and other cellular responses.[2] The human epidermal growth factor receptor-2 (ErbB2, HER2) drives tumor proliferation with downstream signaling through the PI3K-AKT and MEK-ERK pathways.[2,3] HER2 overexpression and amplification has been identified as a poor prognostic marker in a subset of patients diagnosed with breast, gastric or gastroesophageal junction cancer.[2,4] However; agents targeting this pathway have significantly improved the survival of patients with HER2+ breast and gastric cancer.[5-8]

Recently, mutations of the HER2 receptor tyrosine kinase have been identified in several different cancers. These mutations can reside in the kinase domain (D769Y, D769H, L755S, V777L, V842I, or in-frame exon 20 insertions), transmembrane domain (V659E/D, G660D), or the extracellular domain (G309A, G309E, S310F, S310Y or E321G) of HER2[9, 45]. A novel splice variant of HER2 resulting in deletion of exon 16 was also found to be a major oncogenic driver.[46] These mutations have been found in breast, lung, ovarian, and bladder cancers. Evidence supports that at least in some tumors, these mutations function as driver mutations. It is known that 2-4% of NSCLC harbor activating mutations[10-13] and that such mutations are also found in ovarian cancers[14] as well as several other cancer subtypes.[15] Recently, in a small study of 15 micropapillary urothelial carcinoma (MPUC), 40% harbored a HER2 mutations compared to the 9.4% seen in 64 cases of non-MPUC cases.[16] HER2 activating mutations lead to constitutive activation of the receptor and downstream AKT and MEK pathways.[17]

Afatinib dimaleate (hereafter, referred to as afatinib) is a potent and selective, oral irreversible inhibitor of ErbB family members. It is one of several dual EGFR/HER2 targeted agents in clinical development. Afatinib was more effective than erlotinib against EGFR mutant cancers in preclinical models.[18] Afatinib has been reported to have efficacy against HER2 activating mutations. Preclinically, afatinib delayed tumor growth compared to placebo in mice harboring established tumors using the NSCLC cell line NCI-H1781, which has the HER2 776insV mutation.[17] Sensitivity to afatinib with tumor regressions measured by tumor volume was also noted in the transgenic lung cancer HER2 YVMA model.[17] Similarly, afatinib was effective against Ba/F3 cells transformed with various activating HER2 mutations, including extracellular domain mutations.[9] In

these studies, the IC50 of afatinib was comparable to neratinib and more effective than lapatinib.

In vitro efficacy of afatinib has also recently been observed in primary uterine cervical cancer cells harboring activating HER2 extracellular domain mutations (S280F and E375D). This was associated with blockade of cells in G1 phase of the cell cycle and reduced markers of activated HER2 pathway.[19]

Afatinib has been shown to exert clinical activity against tumors harboring ErbB2 (HER2) mutations. In one exploratory phase II study, three patients with lung adenocarcinoma exhibiting activating mutations of HER2 in exon 20 were treated with 50mg/day afatinib.[20] In all three patients, an objective partial response was observed, and time to progression ranged between 3-4 months.

In another study, 65 patients with HER2 mutated (exon 20 insertion) lung cancer were retrospectively identified.[11] In this cohort, 22 evaluable patients who received HER2-directed therapies were analyzed. Interestingly, the disease control rate observed in patients who received afatinib as monotherapy (n=4) was 100%. In contrast, no responses were observed with lapatinib, a EGFR/HER2 reversible inhibitor (n=2), or masatinib (n=1) monotherapy. The remaining 15 patients received trastuzumab in combination with chemotherapy and achieved a disease control rate of 96%.

A rapid and durable complete response following afatinib therapy was also observed in a patient with Li-Fraumeni Syndrome and metastatic adenocarcinoma of the lung harboring synchronous EGFR L858R and HER2 S310F mutations.[21] A separate case report also reported response to lapatinib in combination with chemotherapy in a Li Fraumeni patient with lung cancer possessing a HER2 kinase activating mutation.[22]

A phase II study of trastuzumab pre-treated HER2 positive (amplification or over expression) advanced breast cancer patients (N=41) with afatinib 50mg demonstrated 10% partial response and 37% stable disease. Mean duration of objective response was 153 days.[23]

Recently, 3 of 4 lung adenocarcinoma patients with mutations in the HER2 transmembrane domain (V659 and G660) also had durable clinical responses to Afatinib.[46]

The most up-to-date preclinical and clinical study information for afatinib can be found in the Investigator's Brochure (2014).[25]

1.1.1 Mechanisms of Action and Preclinical Data with Afatinib

Afatinib is a highly potent, irreversible ErbB family blocker. The activity of EGFR, HER2 and HER4 kinases are inhibited with IC50 values of 0.5nM, 14nM and 1nM, respectively (Investigator's Brochure, 2014).[25] Afatinib did not demonstrate significant inhibitory activity in a larger panel of protein kinases and in receptor-ligand binding assays, supporting the selectivity of this compound for the ErbB receptor family. Afatinib was designed to allow covalent binding to specific cysteine residues within the catalytic cleft of the targeted enzymes (Cys 797 in EGFR, Cys 805 in HER2 and Cys 803 in HER4), thus resulting in prolonged duration of action in cellular washout experiments.[25,26]

In preclinical in vitro models, afatinib effectively inhibits ligand-induced EGFR and constitutive HER2 phosphorylation, leading to tumor growth inhibition and regression. When afatinib was evaluated in NSCLC cell lines harboring EGFR kinase activating and resistance mutations, afatinib inhibited receptor activation and proliferation.[27-29] Afatinib also inhibits the proliferation of H1781 NSCLC cells displaying wild type EGFR and mutated HER2 receptors (G776VinsC).[25]

Xenograft and transgenic mouse models have been used to evaluate the anti-tumor activity of afatinib. In mice, afatinib is bioavailable after oral administration and reaches efficacious plasma exposure with once daily dosing.[25] Afatinib induced tumor regression in tumor xenograft models derived from four human cell lines known to co-express ErbB receptors (A431 vulvar carcinoma NCI-N87 gastric carcinoma, SKOV-3 ovarian carcinoma, MDA-MB-453 breast carcinoma) with tumor to control (T/C) ratios of 2-4% at doses 20-30mg/kg/d.[25] Afatinib has also demonstrated activity in the trastuzumab-resistant HER2 positive cell line, SUM-190. In EGFR double mutant (EGFRL858R/T790M) NSCLC xenograft models as well as inducible EGFRL858R/T790M transgenic mice, the tumor/control (T/C) values in the afatinib treated groups ranged from 12-18%.[18,30] Other preclinical studies supporting the use of afatinib in tumors with activating HER2 mutations are mentioned in section 1.1. Preclinical data also support combinations of afatinib with rapamycin, cetuximab, nintedanib (BBF 1120), multiple chemotherapy agents (vinorelbine, docetaxel) and radiation.[17,30-33] In the bladder cancer cell line 5637, which harbors the S310F mutation, afatinib synergized with the MEK inhibitor PD184352 to inhibit cell survival.[9]

Preclinical pharmacokinetics from xenograft models showed that the plasma concentration of afatinib associated with anti-tumor activity ranged from 80-285nM with corresponding AUC 0-24h from 589-3198nMh.[25]

Preclinical toxicity from GLP studies in animals showed no effect on body temperature, general behavior, locomotor activity, respiratory function and no major effects on heart rate and ECG. Non- GLP studies in animals were devoid of CNS and pulmonary effects. The only effect seen on the cardiovascular system was reduced contractility at higher intravenous doses. An effect on renal and liver function was seen with the oral dose of 300mg/kg in rats. Furthermore, a dose-dependent effect on gastrointestinal function was seen, including soft feces, loose stool.

In oral repeat-dose studies in rats and minipigs the main target organs were the skin (mice and rats), the gastrointestinal tract (mice, rats and minipigs) and the kidneys (rat). In the gastrointestinal tract, a dose dependent atrophy of the epithelium and concomitant focal erosions/ulcerations in the stomach of rats and minipigs were observed. Clinically, this was characterized by diarrhea in both species and fecal occult blood in individual minipigs. Whereas atrophy was predominant in the intestinal epithelia of rats and minipigs, in the mouse, hypertrophy and hyperplasia were noted, at plasma levels >2x

that observed in humans. Other organs with epithelial atrophy were the skin, prostate, uterus, and vagina in rats and the upper respiratory tract, the prostate, the seminal vesicles and the cornea of the eyes in minipigs and mice. In addition, the mucinous glands in the gastrointestinal and respiratory tract were atrophic. All these changes were generally minimal to moderate and reversible and are most likely related to the inhibition of the ErbB-signaling by afatinib. In mice, no renal papillary necrosis was observed despite reaching life-threatening toxicity and markedly higher systemic drug exposure compared with rats. The observed reactive neutrophilia was considered secondary to the inflammatory processes in the skin (mice, rats) and the gastrointestinal tract (minipigs).

No indication for cardiotoxicity was observed in the chronic oral repeat-dose toxicity studies up to 26 weeks in rats or 52 weeks in minipigs. However, because a negative inotropic effect (reduced contractility) was observed in pigs given intravenous doses of 6.65 mg/kg afatinib or more, appropriate monitoring of contractility is to be considered in clinical trials.

1.1.2 Clinical Pharmacokinetics (PK) and Activity of Afatinib

1.1.2.1 Clinical Pharmacokinetics

Clinical pharmacokinetic data of afatinib were derived from PK data from Phase I/II and III studies with monotherapy or combinations.

Absorption and distribution: Afatinib plasma concentration-time profiles were comparable for the individual dose groups tested (10 to 100 mg), exhibiting at least biexponential disposition kinetics and increased with increasing doses. A moderate to high variability was observed for the plasma concentrations e.g., for the 40 mg dose group with geometric Coefficient of Variations (gCVs) ranging from 50.8 to 221 %. A similar variability range was observed in the other dose groups ranging from 10 to 100 mg. Maximum plasma concentrations mainly occurred at 2 to 5 hours after drug administration. Afatinib exhibited similar disposition characteristics after oral administration at all dose levels after single dose and at steady state, which could be described by at least biexponential disposition kinetics. In cancer patients, afatinib showed a high apparent volume of distribution during the terminal phase both after single dose and at steady state (Vz/F and Vz/F,ss) which might indicate a high tissue distribution of the drug. However, the respective values should be interpreted with caution as the absolute bioavailability (F) of afatinib in humans is not known. Plasma protein-binding of afatinib in humans was non-saturable up to 500nM. Binding of afatinib to human serum albumin (45mg/L) was moderate (79.6%). Protein binding was not changed in

mild and moderately liver impaired subjects compared to matched healthy controls.

Food Effect: A food effect study comparing the pharmacokinetics of afatinib (40 mg) administered as tablets to cancer patients revealed that absorption was decreased with a reduction of afatinib gMean Cmax and AUC0-∞ values by around 50% and 39%, respectively under fed conditions compared to fasted conditions. Since a statistically significant food effect was observed, afatinib should be taken without food (i.e. food should not be consumed for at least 3 hours before and at least 1 hour after taking afatinib).

Metabolism, excretion, and accumulation: Metabolism is of subordinate role for afatinib in vivo. Apparent total body clearance (CL/F and CL/F,ss) in cancer patients was moderate to high. However, the absolute bioavailability (F) of afatinib in humans is unknown. The contribution of renal excretion to the total body clearance of afatinib was low. The major route of elimination was via feces. Accumulation ratios based on AUC ranged from 2.53 to 3.40 and were higher than the ratios based on Cmax (range of gMean values: 2.00 to 2.67). Using the overall gMean accumulation ratio of AUC (2.77), the accumulation (or effective) half-life can be calculated according to the following formula $t1/2=\tau \cdot \ln 2/\ln(RA,AUC/(RA,AUC-1))$.[34] The respective accumulation half-life value of afatinib is 37 h. This is in line with the overall gMean apparent terminal half-life at steady state in cancer patients, which was 37.2 h). Statistical analysis confirmed that steady state was attained within 8 days of afatinib treatment. Afatinib trough values were stable over the observed treatment period (of 6 months and longer) and their intra-individual variability determined per dose group was moderate (gCVs ranging from 22.19% to 67.50%). See Table 1.

Dose Proportionality: Afatinib displays non-linear pharmacokinetics in the therapeutic dose range as AUC and Cmax values increased slightly more than proportional in the range of 20 to 50 mg (after single dose and multiple dose administration.

PK in Hepatic and Renal Insufficiency: Hepatically mild (Child Pugh A, score of 5 or 6 points) and moderate (Child Pugh B, score of 7 to 9 points) impaired patients received a single oral dose of afatinib 50 mg and were compared to healthy subjects. Overall, exposure of afatinib was similar in patients with mild and moderate liver impairment and in healthy controls. The results are in line with the population PK analysis, which demonstrated no significant impact on afatinib exposure based on clinically laboratory tests indicative of an impaired hepatic function.

Less than 5% of a single dose afatinib is excreted via the kidneys. The safety, pharmacokinetics and efficacy of afatinib have not been studied in patients with renal impairment. In the PopPK analysis, exposure to afatinib slightly increased with lowering the creatinine clearance (CrCL), *i.e*. for a patient with a CrCL of 60 or 30 mL/min exposure ($AUC_{T,ss}$) to afatinib increased by 13% and 42%, respectively, and decreased by 6% and 20% in patients with a CrCL of 90 or 120 mL/min, respectively, compared to a patient with the CrCL of 79 mL/min (median within analyzed population). As the effect sizes were within the observed inter-patient variability of exposure, no dose adjustment is considered necessary in patients with mild or moderate renal impairment.

Population PK: No statistically significant effect was seen based on smoking status, ethnic origin, age, liver metastases or liver function parameters. Predicted individual effects are considered to be mild to moderate for creatinine clearance, gender, body weight, ECOG performance status, alkaline phosphatase, lactate dehydrogenase and total plasma protein levels.

Although several phase II studies used 50 mg daily, the phase I data confirms that Css at 40 mg exceeds IC50 for HER2, thus this will be the starting dose for this subprotocol.[44]

Table 1: Comparison of gMean pharmacokinetic parameters of afatinib in cancer patients for the 20mg, 30mg, 40 mg and 50mg dose group and for the whole dose range (10-100mg) from 5 monotherapy trials[23].

Afatnib BS	20mg		30mg		40mg		50mg		Overall (10 – 100mg)	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean
AUC $_{0\text{-}24}$ [ng·h/mL]	12	119 (56.6)	10	189 (95.9)	30	324 (68.9)	69	459 (68.0)		
AUC $_{t,ss}$ [ng·h/mL]	15	380 (77.2)	8	660 (92.4)	26	631 (85.9)	51	1130 (59.6)		
C_{max} [ng/mL]	13	11.6 (85.1)	10	16.3 (139)	30	25.2 (73.3)	73	40.8 (76.6)		
$C_{max,ss}$ [ng/mL]	15	24.5 (88.5)	8	46.5 (120)	27	38.0 (105)	51	77.0 (63.6)		
t_{max} [h] a	13	3.00 (0.500 - 24.0)	10	2.00 (0.567 - 692)	30	3.98 (0.583 - 9.10)	73	3.13 (0900 - 9.05)	189	3.02 (0.467 - 24.0)
$t_{max,ss}$ [h] a	15	4.98 (0.500 - 9.08)	8	2.01 (0.517 - 4.00)	27	2.98 (0.467 - 23.8)	51	3.82 (1.00 - 7.05)	149	3.00 (0.467 - 23.8)
$t_{1/2}$ [h]	11	22.3 (80.3)	10	21.3 (82.1)	30	26.9 (61.1)	13	21.9 (54.8)	127	21.4 (56.5)
$t_{1/2,ss}$ [h]	15	47.1 (51.6)	7	33.4 (56.8)	23	36.3 (57.1)	7	22.3 (25.4)	100	37.2 (45.5)
CL/F [mL/min]	11	1430 (64.7)	10	1370 (72.9)	30	952 (86.2)	13	1090 (94.0)	127	1050 (76.3)
CL/F,ss [mL/min]	15	877 (77.2)	8	758 (92.4)	25	1070 (87.9)	7	1390 (47.3)	104	898 (89.2)
Vz/F [L]	11	2770 (61.8)	10	2520 (109)	30	2220 (101)	13	2080 (123)	127	1940 (87.7)
Vz/F,ss [L]	15	3570 (107)	7	2000 (67.8)	23	2870 (101)	7	2690 (47.8)	99	2770 (99.3)
R_A,AUC	11	3.14 (27.6)	8	3.40 (83.1)	9	2.53 (48.0)	49	2.61 (59.1)	120	2.77 (63.1)
R_A,C_{max}	12	2.23 (26.5	8	2.67 (98.8)	9	2.08 (57.7)	51	2.00 (69.2)	123	2.11 (70.2)

[a] Median range

Potential for Drug-Drug Interactions: Afatinib at concentrations up to 100 µM did not show potent inhibition of the cytochrome P450 isoenzymes that are most relevant for drug metabolism in human (1A1/2, 2A6, 2B6,2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 4A11). Therefore, drug-drug interactions based on inhibition of P450 enzymes by afatinib are unlikely to occur.[25] Induction of *in vitro* enzyme activity was not found for any of the P450 enzymes tested (1A2, 2B6, 2C8, 2C9, 2C19, 3A4) following treatment with up to 5 µM of afatinib for 48 h. No relevant induction of mRNA levels was observed for the respective enzymes upon treatment with afatinib. Based on the results from this study, metabolic drug-drug interactions of afatinib resulting from induction of cytochrome P450 enzymes are not expected. The co-administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken simultaneously with or 6 h after afatinib but increased the exposure to 20 mg afatinib by 48% (AUC0-∞) and 39 % (Cmax) when administered 1h before afatinib. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % afatinib (AUC0-∞) and 22 % (Cmax), respectively. Therefore, caution should be exercised when combining afatinib with potent P-gp modulators. However, changes in afatinib bioavailability by this kind of drugs are considered mild to moderate and do not require any adjustment to the starting dose.

Rev. Add13

1.1.2.2 Clinical Activity

Monotherapy studies in advanced NSCLC:

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.

Previously, on July 12, 2013, the U.S. Food and Drug Administration (FDA) approved afatinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations detected by an FDA-approved test (U.S. Food and Drug Administration, 2013).[24]

Two open-label phase III trials have evaluated afatinib 40mg vs standard platinum-based doublet chemotherapy in first-line treatment of EGFR mutation positive advanced NSCLC patients.[35,36] In both studies, afatinib significantly prolonged PFS compared to chemotherapy (11.1 vs 6.9 mo, HR 0.58; 95% CI 0.43-0.78; p=0.004 and 11.0 vs. 5.6mo HR 0.28; 95%CI 0.2-0.39; p< 0.0001. In those with common EGFR mutations, the PFS improved to a greater

extent (13.6mo vs 6.9mo; HR 0.47; p< 0.0001 and 11.1 vs 5.6mo, HR 0.25; p< 0.0001). A separate randomized, double-blind, placebo- controlled phase IIb/III trial, compared afatinib 50mg po qd to placebo in EGFR tyrosine kinase inhibitor (TKI) pre-treated patients with advanced NSCLC.[37] Although no difference in OS was noted (10.8 vs 12mo) comparing afatinib to placebo, secondary endpoints favored afatinib including progression-free survival, ORR and HRQoL.[37,38]

Afatinib has been shown to exert clinical activity against tumors harboring ErbB2 (HER2) mutations. In one exploratory phase II study, three patients with lung adenocarcinoma exhibiting activating mutations of HER2 in exon 20 were treated with 50mg/day afatinib.[20] In all three patients, an objective partial response was observed, and time to progression ranged between 3-4 months. In another study, 65 patients with HER2 mutated (exon 20 insertion) lung cancer were retrospectively identified.[11] In this cohort, 22 evaluable patients who received HER2-directed therapies were analyzed. Interestingly, the disease control rate observed in patients who received afatinib as monotherapy (n=4) was 100%. In contrast, no responses were observed with lapatinib, a EGFR/HER2 reversible inhibitor (n=2), or masatinib (n=1) monotherapy. The remaining 15 patients received trastuzumab in combination with chemotherapy and achieved a disease control rate of 96%.

<u>Monotherapy studies in solid tumor malignancies other than NSCLC:</u>

Kwak et al studied afatinib in patients with solid tumors (gastric, gastroespophageal, esophageal, biliary, or gallbladder, transitional cell urothelial or gynecological) and either EGFR or HER2 amplification, or EGFR activating mutation in archival tumor tissue (NSCLC was excluded). Of 38 FISH positive tumors, 29 had HER2 amplification. Of the 388 patients, 20 received afatinib. Of these, 13 had HER2 amplification (10high-level, 2 low level). The response rate was 5% (one CR) in this group - a woman with high HER2 amplification in endometrial carcinoma. The trial was terminated early because of recruitment challenges. Eight patients (40%) of HER2 amplified patients had stable disease as best response.[39]

In a phase II open-label trial in patients (N=124) with advanced squamous head and neck cancer not pre-screened for target, patients were randomized (1:1) to afatinib 50mg daily vs. cetuximab (250mg/m^2/week). The primary endpoint was maximum tumor shrinkage from baseline before crossover. Mean tumor shrinkage by independent central review was 16.6% and 10.1% for

afatinib and cetuximab, respectively (p=0.30) and disease control rate was also similar in the two groups.[40] In a phase III trial in patients with recurrent/metastatic HNSCC, after progression on/after platinum-based therapy patients were randomized 2:1 to oral treatment with afatinib 40mg daily (322 patients) or intravenous methotrexate 40mg/m2 weekly (161 patients).[41] There was significant improvement in the primary endpoint of PFS with afatinib (median 2.6 vs 1.7 months; p = 0.03), the disease control rate was higher with afatinib (49.1% vs 38.5%; p=0.035) and afatinib showed delay in deterioration of global health status, pain and swallowing (all p ≤ 0.03), and provided improvement in pain. The most frequent grade 3/4 drug-related adverse events were rash/acne (9.7%) and diarrhea (9.4%) with afatinib.

In metastatic HER2 negative breast cancer, no objective responses were observed in 50 patients treated with afatinib, although 3 patients with triple negative breast cancer showed disease stabilization for 4 months and longer.[42]

In patients with glioblastoma multiforme, the phase II portion of a phase I/II study randomized 119 patients to afatinib monotherapy vs afatinib with temozolomide vs temozolomide alone. PFS at 6 months by investigator assessment was 3%, 10% and 23%, respectively. One patient (2.4%) in the afatinib arm had a PR.[43]

Afatinib has been shown to exert clinical activity against tumors harboring ErbB2 (HER2) mutations

1.1.3 Afatinib Safety Profile

A **Comprehensive Adverse Events and Potential Risks (CAEPR)** list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 3.3 of the protocol.

Based on phase I studies, the MTD for continuous administration of single agent oral afatinib was 50mg or 40mg daily. The data from the monotherapy trials indicate that the safety profile of afatinib is characterized by significant incidence of dose-dependent gastrointestinal and skin toxicities. The most common toxicities seen are: diarrhea, rash/acne and stomatitis. The majority of these are low grade (grade 1-2).

AEs of special interest

Diarrhea, rash, stomatitis and ILD are considered AEs of special interest because they are either known class effects (*i.e.*, have been observed with other EGFR inhibitors) or are potentially life-threatening (Investigator's Brochure, 2014). The following sections provide integrated summaries for these AEs across different clinical trials, with emphasis on trials using afatinib as monotherapy, especially at the RP2D.

Section 3.4 of the protocol has dose modification guidelines for toxicities.

Diarrhea

Diarrhea is the most common AE observed across afatinib monotherapy trials, typically affecting > 80% of patients. Grade 3 diarrhea with the 40mg po qd dose was 15.3% vs 17.2% with the 50mg po qd dose. The majority of patients (> 70%) experienced diarrhea within 14 days of starting afatinib. Grade 3 diarrhea most frequently occurred within the first 6 weeks of treatment. Risk factors for grade 3 diarrhea included: low body weight (< 50kg), females, and low baseline renal function (CrCl < 80mL/min). SAE of diarrhea were reported in 4-7% of patients and grade 5 diarrhea has been reported. Dehydration and renal impairment have both been reported related to diarrhea. Proactive management of diarrhea including adequate hydration and antidiarrheal agents (i.e. loperamide) is important and should be started at first signs of diarrhea.

Rash/Acne

Rash/acne is one of the most common AE reported in patients on afatinib trials with the total incidence reaching 90% in the pivotal NSCLC trial using afatinib monotherapy at 40mg po qd. Grade 3 rash/acne was similar at 40mg and 50mg (14 and 16.2%, respectively). In general, rash manifests as a mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to sun. The majority of patients experienced onset of rash/acne within the first 4 weeks of treatment (79.7% at 40mg and 65.1% at 50mg). Risk factors for grade 3 events included low body weight (< 50kg) and low baseline renal function(<80mL/min). Protective clothing, and/or use of sun screen is advisable. Early intervention (e.g. emollients, antibiotics) of dermatologic reaction is also recommended. Dose reduction allowed successful management of rash in the majority of cases. Rare cases of bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome. Afatinib should be interrupted or discontinued if these occur.

Palmar-plantar erythrodysaesthesia syndrome was also reported as a dermatologic AE with afatinib at rates of 6.6-7.7%. The majority were grade 1-2, but grade 3 events have been reported.

Interstitial Lung disease (ILD)

ILD or ILD-like events are a well-described, infrequent risk of EGFR inhibitors. There have been reports of ILD or ILD-like events in 1.5% of afatinib treated patients. The rate of these events is similar to that observed with other EGFR inhibitors. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude ILD. Treatment should be interrupted pending investigation of these symptoms. If ILD is diagnosed, afatinib should be permanently discontinued and appropriate treatment instituted as necessary.

Hepatic Adverse Events

Hepatic AEs include elevated hepatic enzymes, which are primarily grade 1-2 and did not lead to treatment discontinuation. In the entire afatinib exposed population, 10.8% (95% CI 10.1-11.7%) were reported with AEs indicative of hepatic impairment with 8 pts with hepatic AEs leading to death. These were considered not related to afatinib in 5 patients (related to progressive disease or sepsis). Drug-related fatal case of acute hepatic failure has been reported. Periodic liver function testing is recommended in patients treated with afatinib.

Keratitis

Keratitis and ulcerative keratitis have been reported with the EGFR inhibitors. In 6,002 afatinib treated patients, 39 (0.6%) cases were identified.

Effect on QTc

A phase II study in patients with advanced solid tumors investigated the effect of afatinib on the QTc interval. Afatinib at doses of 50mg daily did not prolong the QT interval or the heart rate corrected QT interval (QTcF). It did not affect heart rate. No other clinically meaningful changes in QTcF or ECG endpoints were observed.

Events of cardiac dysfunction/LVEF decrease

Left ventricular ejection fraction (LVEF) decrease has been reported with agents targeting HER2, in particular with the monoclonal antibody, trastuzumab. In the phase IIb/III trial in advanced NSCLC using afatinib 50mg, 4 (1.0%) afatinib treated patients vs 1 (0.5%) placebo patients experienced an AE of cardiac failure, cardiopulmonary failure, hepatic congestion or left heart failure. This was a non-significant difference (HR 1.32, 0.14-12.50).[37] In study 1200.32, with 40mg of afatinib, the frequency of these AEs was 2.6% in the afatinib arm vs 0.9% in the chemotherapy arm. This was not significantly increased when corrected for time at risk (HR 1.18, 0.12-11.39). Furthermore, the heart failure or LVEF decrease events were all grade 2 or lower.[35]

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.2/16
Rev.Add13 _____ 2.1.2 Patient's tumor must have activating HER2 mutation, as determined via the MATCH Master Protocol and according to Appendix III.

Additionally, any in-frame insertions in exon 20 will be considered an activating mutation. 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 diarrhea at baseline.

_____ 2.1.7 Patients with a history of interstitial lung disease will be excluded.

_____ 2.1.8 Patients must not have had prior treatment with any of the following TKIs, which have known activity against HER2 kinase:

- Neratinib
- AC-480 (BMS-599626)
- AST 1306
- Canertinib (CI 1033)
- CUDC-101
- Lapatinib
- TAK285
- Afatinib
- AEE 788
- AZD8931
- CP-724714
- Dacomitinib
- Perlitinib

_____ 2.1.9 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.

_____ 2.1.10 Patients with non-small cell lung cancer will be excluded.

_____ _____

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

3.1 Administration Schedule

Patients will be instructed to take afatinib 40mg PO daily at the same time each day continuously for each 28 day cycle until tumor progression or unless patient experiences unacceptable toxicities.

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.

3.1.1 Potential Drug-drug interaction

Afatinib is a substrate of P-glycoprotein (P-gp). Thus, in patients taking P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone), or strong P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's Wort), which may alter exposure to afatinib, afatinib should be administered simultaneously with or before drugs that affect P-gp.

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.

3.2 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 instructions, requirements and exceptions for EAY131 – Subprotocol B

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 B 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 B specific expedited reporting exceptions:

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

- If an AE meets the reporting requirements 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
Rev. Add21

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Afatinib (BIBW 2992, 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 requirements 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 2.2, April 24, 2019[1]

Adverse Events with Possible Relationship to Afatinib (CTCAE 5.0 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 disorders)[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)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
Infection[4]			***Infection[4] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		

Adverse Events with Possible Relationship to Afatinib (CTCAE 5.0 Term) [n= 2596]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased		
	Creatinine increased[5]		
		Ejection fraction decreased	
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypokalemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		
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)***
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

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 failure; Respiratory, thoracic and mediastinal disorders - Other (nasal dryness); 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.

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. With the 50 mg dose used in previous trials of afatinib in HER2+, patients showed poor tolerability data. 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 longer 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 > 7 days. 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*

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 used 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 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: 40 mg po once daily

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.

Rev. 3/17

7. References

1. Olayioye MA, Neve RM, Lane HA, et al: The ErbB signaling network: receptor heterodimerization in development and cancer. The EMBO journal 19:3159-67, 2000
2. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177-82, 1987
3. Spector NL, Blackwell KL: Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27:5838-47, 2009
4. Begnami MD, Fukuda E, Fregnani JH, et al: Prognostic implications of altered human epidermal growth factor receptors (HERs) in gastric carcinomas: HER2 and HER3 are predictors of poor outcome. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 29:3030-6, 2011
5. Bang YJ, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376:687-97, 2010
6. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. The New England journal of medicine 353:1673-84, 2005
7. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. The New England journal of medicine 344:783-92, 2001
8. Swain SM, Kim SB, Cortes J, et al: Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 14:461-71, 2013
9. Greulich H, Kaplan B, Mertins P, et al: Functional analysis of receptor tyrosine kinase mutations in lung cancer identifies oncogenic extracellular domain mutations of ERBB2. Proceedings of the National Academy of Sciences of the United States of America 109:14476-81, 2012
10. Arcila ME, Chaft JE, Nafa K, et al: Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clinical cancer research : an official journal of the American Association for Cancer Research 18:4910-8, 2012
11. Mazieres J, Peters S, Lepage B, et al: Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31:1997-2003, 2013

12. Shigematsu H, Takahashi T, Nomura M, et al: Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Research 65:1642-6, 2005
13. Tomizawa K, Suda K, Onozato R, et al: Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. Lung Cancer 74:139-44, 2011
14. Anglesio MS, Arnold JM, George J, et al: Mutation of ERBB2 provides a novel alternative mechanism for the ubiquitous activation of RAS-MAPK in ovarian serous low malignant potential tumors. Molecular cancer research : MCR 6:1678-90, 2008
15. Chmielecki J, Ross JS, Wang K, et al: Oncogenic Alterations in ERBB2/HER2 Represent Potential Therapeutic Targets Across Tumors From Diverse Anatomic Sites of Origin. The Oncologist, 2014
16. Ross JS, Wang K, Gay LM, et al: A high frequency of activating extracellular domain ERBB2 (HER2) mutation in micropapillary urothelial carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 20:68-75, 2014
17. Perera SA, Li D, Shimamura T, et al: HER2YVMA drives rapid development of adenosquamous lung tumors in mice that are sensitive to BIBW2992 and rapamycin combination therapy. Proceedings of the National Academy of Sciences of the United States of America 106:474-9, 2009
18. Li D, Ambrogio L, Shimamura T, et al: BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene 27:4702-11, 2008
19. Lopez S, Cocco E, Stefania B, et al: Afatinib, an irreversible ErbB family inhibitor, demonstrates activity against HER2 mutated cervical cancer in vitro, 105th Annual Meeting of the American Association for Cancer Research. San Diego, CA, Cancer Research, 2014
20. De Greve J, Teugels E, Geers C, et al: Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer 76:123-7, 2012
21. Jia Y, Ali SM, Saad S, et al: Successful treatment of a patient with Li-Fraumeni syndrome and metastatic lung adenocarcinoma harboring synchronous EGFR L858R and ERBB2 extracellular domain S310F mutations with the pan-HER inhibitor afatinib. Cancer biology & therapy 15:970-4, 2014
22. Serra V, Vivancos A, Puente XS, et al: Clinical response to a lapatinib-based therapy for a Li-Fraumeni syndrome patient with a novel HER2V659E mutation. Cancer discovery 3:1238-44, 2013
23. Lin NU, Winer EP, Wheatley D, et al: A phase II study of afatinib (BIBW 2992), an irreversible ErbB family blocker, in patients with HER2-positive metastatic breast cancer progressing after trastuzumab. Breast Cancer Research and Treatment 133:1057-65, 2012
24. United States FDA: Afatinib, 2013
25. Investigator's Brochure. BIBW 2992 (afatinib). Boehringer Ingelheim. Version 15. , 2014
26. Bridges AJ: Chemical inhibitors of protein kinases. Chemical Reviews 101:2541-72, 2001

27. Carter TA, Wodicka LM, Shah NP, et al: Inhibition of drug-resistant mutants of ABL, KIT, and EGF receptor kinases. Proceedings of the National Academy of Sciences of the United States of America 102:11011-6, 2005

28. Kwak EL, Sordella R, Bell DW, et al: Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. Proceedings of the National Academy of Sciences of the United States of America 102:7665-70, 2005

29. Solca F, Schweifer N, Baum A, et al: BIBW 2992, an irreversible dual EGFR/HER2 kinase inhibitor, shows activity on L858R/T790M EGFR mutants. , AACR-NCI-EORTC International Conference 'Molecular Targets and Cancer Therapeutics: Discovery, Biology, and Clinical Applications'. Philadelphia, Clinical Cancer Research, 2005

30. Regales L, Gong Y, Shen R, et al: Dual targeting of EGFR can overcome a major drug resistance mutation in mouse models of EGFR mutant lung cancer. The Journal of clinical investigation 119:3000-10, 2009

31. Inoue K, Slaton JW, Perrotte P, et al: Paclitaxel enhances the effects of the anti-epidermal growth factor receptor monoclonal antibody ImClone C225 in mice with metastatic human bladder transitional cell carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 6:4874-84, 2000

32. Janjigian Y, Groen H, Horn L, et al: Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib., 47th Ann Mtg of the American Society of Clinical Oncology (ASCO),. Chicago, Journal of Clinical Oncology 2011

33. Poindessous V, Ouaret D, El Ouadrani K, et al: EGFR- and VEGF(R)-targeted small molecules show synergistic activity in colorectal cancer models refractory to combinations of monoclonal antibodies. Clinical cancer research : an official journal of the American Association for Cancer Research 17:6522-30, 2011

34. Heise T, Graefe-Mody EU, Huttner S, et al: Pharmacokinetics, pharmacodynamics and tolerability of multiple oral doses of linagliptin, a dipeptidyl peptidase-4 inhibitor in male type 2 diabetes patients. Diabetes, obesity & metabolism 11:786-94, 2009

35. Sequist LV, Yang JC, Yamamoto N, et al: Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31:3327-34, 2013

36. Wu YL, Zhou C, Hu CP, 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. The Lancet. Oncology 15:213-22, 2014

37. 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. The Lancet. Oncology 13:528-38, 2012

38. Hirsh V, Cadranel J, Cong XJ, et al: Symptom and quality of life benefit of afatinib in advanced non-small-cell lung cancer patients previously treated with erlotinib or gefitinib: results of a randomized phase IIb/III trial (LUX-Lung 1). Journal of thoracic

oncology : official publication of the International Association for the Study of Lung Cancer 8:229-37, 2013

39. Kwak EL, Shapiro GI, Cohen SM, et al: Phase 2 trial of afatinib, an ErbB family blocker, in solid tumors genetically screened for target activation. Cancer 119:3043-51, 2013
40. Seiwert TY, Fayette J, Cupissol D, et al: A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 25:1813-20, 2014
41. Machiels J, Haddad RI, Fayette J, et al: Afatinib vs Methotrexate in Second-Line Treatment of Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma, ESMO, 2014
42. Schuler M, Uttenreuther-Fischer M, Piccart-Gebhart M, et al: BIBW 2992, a novel irreversible EGFR/HER1 and HER2 tyrosine kinase inhibitor, for the treatment of patients with HER2-negative metastatic breast cancer after failure of no more than two prior chemotherapies. , 46th Annual Meeting of ASCO. Chicago, Journal of Clinical Oncology, 2010
43. Reardon DA, Nabors LB, Mason WP, et al: Phase I/randomized phase II study of afatinib, an irreversible ErbB family blocker, with or without protracted temozolomide in adults with recurrent glioblastoma. Neuro-oncology, 2014
44. Gordon MS, Mendelson DS, Gross M, et al: A Phase I, open-label, dose-escalation study of continuous once-daily oral treatment with afatinib in patients with advanced solid tumors. Investigational New Drugs 31:409-16, 2013
45. Ou SI, Schrock AB, Bocharov EV, et al: HER2 Transmembrane Domain (TMD) Mutations (V659/G660) That Stabilize Homo- and Heterodimerization Are Rare Oncogenic Drivers in Lung Adenocarcinoma That Respond to Afatinib. J Thorac Oncol 16: 33532-8, 2016
46. Turpin J, Ling C, Crosby EJ, et al: The ErbB2ΔEx16 splice variant is a major oncogenic driver in breast cancer that promotes a pro-metastatic tumor microenvironment. Oncogene 35: 6053-64, 2016

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

Rev. 3/17

Appendix I

Rev.12/16

Patient Pill Calendar

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 Month	Day	Year	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.)
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 B: 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 B: Afatinib

Rev.2/16, 3/17

Appendix III

Rev.12/16
Rev. 5/16
Rev.Add13

Actionable Mutations of Interest (aMOIs)

Inclusion Variants

A function has been implemented in MATCHBOX to identify any novel in-frame insertions in exon 20 of the ERBB2 gene at Level of Evidence code 2. This function also includes any putative activating mutations in exon 20 of the ERBB2 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	aMOI
ERBB2	COSM1251412	SNV	2	p.D769Y
ERBB2	COSM12556	Large Indel	2	p.V777_G778insGSP
ERBB2	COSM13170	SNV	2	p.D769H
ERBB2	COSM14060	SNV	2	p.L755S
ERBB2	COSM14062	SNV	2	p.V777L
ERBB2	COSM14065	SNV	2	p.V842I
ERBB2	COSM20959	Large Indel	2	p.A775_G776insYVMA
ERBB2	COSM35764	SNV	3	p.E321G
ERBB2	COSM436496	SNV	3	p.G309A
ERBB2	COSM48358	SNV	3	p.S310F
ERBB2	COSM94224	SNV	3	p.G309E
ERBB2	COSM94225	SNV	3	p.S310Y
ERBB2	COSM682	Large Indel	2	p.E770_A771insAYVM
ERBB2	COSM12558	Large Indel	2	p.A771_Y772insYVMA
ERBB2	OMINDEL569	Indel	2	p.G776delinsVC
ERBB2	COSM85995	Indel	2	p.G776delinsVC
ERBB2	COSM12553	Indel	2	p.G776delinsVC
ERBB2	COSM12552	Indel	2	p.G776delinsVC
ERBB2	COSM12555	Large Indel	2	p.V777_G778insGSP
ERBB2	COSM303948	Large Indel	2	p.V777_G778insGSP
ERBB2	COSM303939	Large Indel	2	p.V777_G778insCG
ERBB2	COSM26681	Indel	2	p.G778_S779insG
ERBB2	COSM681	Large Indel	2	p.S779_P780insVGS
ERBB2	COSM51317	SNV	3	p.I767M
ERBB2	COSM3724566	SNV	3	p.V659E
ERBB2	COSM4681497	SNV	3	p.G660D
ERBB2	COSM4849559	SNV	3	p.G660R
ERBB2	COSM436500	SNV	3	p.V777L
ERBB2	COSM436498	SNV	3	p.678Q