3. Afatinib Treatment Plan

3.1 Administration Schedule

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

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

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

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

3.2 Adverse Event Reporting Requirements

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

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

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

Additional Instructions

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

EAY131 – Subprotocol A specific expedited reporting requirements:

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

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 <u>second malignancy</u> 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 <u>secondary malignancy</u> 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.

3.3 <u>Comprehensive Adverse Events and Potential Risks List (CAEPR) for Afatinib (NSC 750691)</u>

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2596 patients.* Below is the CAEPR for Afatinib.

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

Version 2.1, October 10, 2016[1]

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

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

Adverse Events with Possible Relationship to Afatinib (CTCAE 4.0 Term) [n= 2596]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Skin and subcutaneous tissue disorders - Other (rash)[8]			***Skin and subcutaneous tissue disorders - Other (rash)[8] (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

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

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

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

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Bone marrow hypocellular

EAR AND LABYRINTH DISORDERS - Vertigo

GASTROINTESTINAL DISORDERS - Abdominal pain; Dry mouth; Dysphagia; Esophageal stenosis; Esophagitis; Gastritis; Gastroesophageal reflux disease; Oral pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Malaise;
Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure

IMMUNE SYSTEM DISORDERS - Allergic reaction

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Ejection fraction decreased; GGT increased; INR increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Myalgia; Pain
in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Lethargy; Seizure

PSYCHIATRIC DISORDERS - Confusion; Insomnia

RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Proteinuria

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Female genital tract fistula; Pelvic pain

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

SKIN AND CUTANEOUS TISSUE DISORDERS - Alopecia

VASCULAR DISORDERS - Hypotension; Vasculitis

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

3.4 Dose Modifications

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

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version

4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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

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

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

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

Table 1. Dose Levels for Afatinib

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

3.4.1 Treatment compliance

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

3.4.2 Toxicity monitoring & dose modification

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

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

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

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

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

3.4.3 Dose reduction for afatinib

Intra-patient dose reduction by 1, and if needed 2, dose-levels will be allowed depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal from

study treatment have not been met. Intrapatient dose re-escalation is not allowed.

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

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

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

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

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

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

a. *No dose modifications will be needed for low electrolytes (Na, K, Phos, Mg) unless the grade 3 or 4 adverse event were to last > 48 hours despite optimal electrolyte repletion*
b. *See supportive care for diarrhea in Section 3.5.1*
c. *Nausea and vomiting should be graded after maximal medical management*
d. *See supportive care for rash in Section 3.5.1*

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

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

3.5 Supportive Care

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

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

Management of Diarrhea

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

The recommendations for management are as follows:

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

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.

4. Study Parameters

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).

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.

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

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.

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.

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

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

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

I. As clinically indicated

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

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)