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

EAY131-Z1A

# Molecular Analysis for Therapy Choice (MATCH)

# MATCH Treatment Subprotocol Z1A: Binimetinib in Patients with Tumors (Other Than Melanoma) with NRAS Mutations


| | |
|---|---|
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**Version Date:** May 16, 2018


**NOTE: This subprotocol (EAY131-Z1A) 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***

May 31, 2016 (incorporated in Addendum #3)
Addendum #5 – 12/16
Addendum #6 – 1/17
Addendum #7 – 3/17
Addendum #13

| Agent | IND# | NSC# | Supply |
|---|---|---|---|
| Binimetinib | IND Sponsor: DCTD | 788187 | NCI Supplied |

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## Schema


Cycle = 28 days
Accrual Goal: 70

# 1. Introduction

## 1.1 Binimetinib

Binimetinib (MEK162, ARRY-162) is a potent and selective oral inhibitor of MEK1 and MEK2. It is a non-ATP-competitive allosteric inhibitor that has an 12 nanomolar $IC_{50}$ against purified MEK enzyme[1]. Preclinical studies demonstrated that binimetinib had significant activity, $IC_{50}$ from 30 to 250 nanomolar, in B-RAF and RAS mutated cell lines[1]. A phase 1 trial demonstrated that binimetinib is well tolerated and has an MTD of 60mg twice daily[2]. However, because of retinal toxicity at 60mg twice daily, subsequent phase 2 and 3 trials have adapted a binimetinib dose of 45mg twice daily. The dose limiting toxicities of binimetinib were rash and central serous retinopathy[2]. Other common toxicities seen on the phase 1 include diarrhea, nausea, and peripheral edema [2]. More rare toxicities include elevated CK and decreaesd left ventricular function. The half life of the drug was approximately 5 hours[2]. Skin biopsies performed on patients receiving binimetinib demonstrated decreased pERK activity[2].

## 1.2 Supporting Preliminary Data

RAS mutations result in upregulation of the mitogen-activated protein kinase (MAPK) pathway and are thought to be key driver mutations in many malignancies[3]. The importance of RAS mutations is underscored by its high prevalence in human malignancies. Data from the COSMIC database indicates that RAS, which has three highly homologous isoforms KRAS, N-RAS, and H-RAS, is mutated in approximately 30% of human malignancies[4]. Mutations in NRAS are found in approximately 8% of human cancers[4]. While most frequently seen in melanomas, NRAS mutations are seen in many other solid malignancies including colorectal, gastric, thyroid, uterine endometrial, lung, among others[5-10].

Despite enormous efforts from both academia and industry, successful targeting of RAS mutated malignancies has been an elusive goal[11]. Clinical trials testing numerous strategies, including farnesyl transferase inhibitors and combined MEK/PI3K inhibition, have failed to produce widespread, clinically meaningful results. Interestingly, preclinical testing demonstrates that NRAS mutated cell lines are more sensitive to MEK inhibitor than KRAS mutated cell lines[12,13]. For example, a study of lung cancer cell lines demonstrated that five of six NRAS-mutant cell lines were sensitive to the MEK inhibitors [12].

Consistent with *in vitro* observations,, the most successful effort in targeting RAS mutations has been seen in NRAS mutated melanoma. In an open label phase 2 study, treatment of 117 patients with NRAS mutated melanoma with the MEK inhibitor binimetinib resulted in an overall response rate of 14.5% with PFS of 3.6 months and OS of 12.2 months[14]. In a smaller phase 2 trial of binimetinib, six (20%; 95% CI 8-39%) of 30 patients with NRAS-mutated melanoma had a partial response[15]. An ongoing phase 3 study randomizes patients with NRAS mutated melanoma to binimetinib versus dacarbazine with a primary endpoint of PFS; enrollment is complete and results are awaited. Our trial will test the hypothesis that inhibition of MEK with binimetinib is an effective therapy in NRAS mutated malignancies.

## 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 Registration to Treatment

_____ 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).

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_____ 2.1.2 Patients must have NRAS mutation in codon 12, 13, 61 as determined via the MATCH Master Protocol. See Appendix II for a list of the specific variants and corresponding Levels of Evidence.

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

Date of ECG: _____

_____ 2.1.4 Patients must have adequate bone marrow, organ function and laboratory parameters

- Creatinine ≤ 1.5 mg/dL, or calculated creatinine clearance (determined as per Cockcroft-Gault) ≥ 50mL/min;

_____ 2.1.5 Patients must have adequate cardiac function:

- left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram,
- QTc interval ≤ 480 ms

_____ 2.1.6 Patients must not have known hypersensitivity to binimetinib or compounds of similar chemical or biologic composition.

_____ 2.1.7 Patients with melanoma are excluded.

_____ 2.1.8 Patients must not have any active central nervous system (CNS) lesion (i.e., those with radiographically unstable, symptomatic lesions) and/or leptomeningeal metastases.

**NOTE:** Patients treated with stereotactic radiotherapy or surgery are eligible if the patient remained without evidence of CNS disease progression ≥ 3 months. Patients must be off corticosteroid therapy for ≥ 3 weeks.

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_____ 2.1.9 Patients must not have a history or current evidence of retinal vein occlusion (RVO) or predisposing factors to RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes). Please refer to Safety and Tolerability Assessments in Section 3.4 for more information.

_____ 2.1.10 Patients must not have a history of retinal degenerative disease.

_____ 2.1.11 Patients must not have a history of Gilbert's syndrome.

_____ 2.1.12 Patients must not have uncontrolled arterial hypertension despite medical treatment.

_____ 2.1.13 Patients must not have active hepatitis B, and/or active hepatitis C infection.

_____ 2.1.14 Patients must not have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

_____ 2.1.15 Patients must not have impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).

_____ 2.1.16 Patients who have received prior MEK inhibitors are excluded.

_____ _____

Physician Signature Date

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

## 3. Binimetinib Treatment Plan

### 3.1 Administration Schedule

This is an open label single arm study testing binimetinib in patients with NRAS mutated malignancies. Each patient will be treated with orally administered binimetinib 45mg twice daily continuously throughout the trial. Patients will continue on the binimetinib until disease progression or unacceptable toxicity. A cycle is defined as 28 days.

Each dose of binimetinib should be taken with a glass of water (with or without food). Missed or vomited doses of binimetinib will not be replaced.

### 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 protocol EAY131 – Subprotocol Z1A

**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 Z1A 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 binimetinib, or within 28 days of the subject's last dose of binimetinib, 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 Z1A specific expedited reporting exceptions:**

For Subprotocol Z1A, 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.

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Binimetinib (NSC 788187)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. 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 (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 662 patients.* Below is the CAEPR for Binimetinib.

**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 2.0, March 2, 2016**[1]

| **Adverse Events with Possible Relationship to Binimetinib (CTCAE 4.0 Term) [n= 662]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | ***Anemia (Gr 2)*** |
| CARDIAC DISORDERS | | | |
| | | Heart failure | |
| EYE DISORDERS | | | |
| | Blurred vision | | ***Blurred vision (Gr 2)*** |
| | Eye disorders - Other (retinopathy)[2] | | |
| | | Eye disorders Other - (retinal vein occlusion) | |
| | Eye disorders Other - (visual disorder)[3] | | |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | ***Abdominal pain (Gr 2)*** |
| | Constipation | | ***Constipation (Gr 2)*** |
| Diarrhea | | | ***Diarrhea (Gr 2)*** |
| | Mucositis oral | | ***Mucositis oral (Gr 2)*** |
| Nausea | | | ***Nausea (Gr 2)*** |
| | Vomiting | | ***Vomiting (Gr 2)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Edema face | | |
| Edema limbs | | | ***Edema limbs (Gr 2)*** |
| Fatigue | | | ***Fatigue (Gr 2)*** |

| | | | |
|---|---|---|---|
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased (Gr 2)*** |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased (Gr 2)*** |
| CPK increased[4] | | | ***CPK increased[4] (Gr 2)*** |
| | Ejection fraction decreased | | |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia (Gr 2)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | ***Arthralgia (Gr 2)*** |
| | Back pain | | ***Back pain (Gr 2)*** |
| | Myalgia | | ***Myalgia (Gr 2)*** |
| | | Musculoskeletal and connective tissue disorders - Other (rhabdomyolysis) | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Dyspnea | | |
| | | Pneumonitis | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Alopecia | | ***Alopecia (Gr 2)*** |
| | Dry skin | | ***Dry skin (Gr 2)*** |
| | Pruritus | | ***Pruritus (Gr 2)*** |
| Rash acneiform | | | ***Rash acneiform (Gr 2)*** |
| Rash[5] | | | ***Rash[5] (Gr 2)*** |
| VASCULAR DISORDERS | | | |
| | Hypertension | | ***Hypertension (Gr 2)*** |
| | Hemorrhage[6] | | |

[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] Retinopathy may include chorioretinopathy, chorioretinitis, and retinal detachment.

[3]Visual disorders may include visual disturbance, blurred vision, visual acuity reduced, flashing light, and floaters.

[4]CPK increased may be associated with muscle pain and muscle weakness.

[5]Rash may include rash maculo-papular and erythematous rash.

[6]The majority of hemorrhage events were mild, although serious bleeding events in the eyes, GI tracts or lungs have rarely been reported.

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

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Febrile neutropenia

**CARDIAC DISORDERS** - Atrial fibrillation; Atrioventricular block complete; Cardiac disorders - Other (tachycardia); Myocardial infarction; Palpitations

**ENDOCRINE DISORDERS** - Hypothyroidism

**GASTROINTESTINAL DISORDERS** - Ascites; Cheilitis; Dyspepsia; Gastritis; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (pneumatosis intestinalis); Ileus; Oral hemorrhage; Retroperitoneal hemorrhage; Small intestinal obstruction; Small intestinal perforation

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema trunk; Fever; Flu like symptoms; General disorders and administration site conditions - Other (generalized edema); Multi-organ failure

**HEPATOBILIARY DISORDERS** - Hepatic failure

**INFECTIONS AND INFESTATIONS** - Lung infection; Paronychia; Pharyngitis; Sepsis; Skin infection

**INVESTIGATIONS** - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight loss

**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hyperglycemia; Hypoalbuminemia; Hypoglycemia; Hypokalemia; Hyponatremia; Tumor lysis syndrome

**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor pain

**NERVOUS SYSTEM DISORDERS** - Akathisia; Dizziness; Headache; Intracranial hemorrhage; Nervous system disorders - Other (dropped head syndrome); Paresthesia; Somnolence; Syncope; Transient ischemic attacks

**PSYCHIATRIC DISORDERS** - Insomnia; Suicide attempt

**RENAL AND URINARY DISORDERS** - Acute kidney injury; Hematuria; Proteinuria

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Atelectasis; Cough; Epistaxis; Pleural effusion; Pneumothorax; Pulmonary hypertension; Respiratory failure; Wheezing

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (skin burning sensation)

**VASCULAR DISORDERS** - Hypotension; Venous thromboembolism

**NOTE:** Binimetinib 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

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## 3.4 Dose Modifications

The initial dose of each patient will be binimetinib 45mg twice daily. Patients who develop study drug related toxicity can reduce the dose of binimetinib to 30mg twice daily. Dose reductions below to binimetinib 30mg twice daily are not allowed.

When the AE that resulted in a dose reduction improves to and remains stable at the patient's Baseline for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant binimetinib-related toxicities that would prevent drug re-escalation. There is no limit to the number of times the patient can have their dose reduced or re escalated (in 15 mg increments); however, no dose re escalation is allowed after a dose reduction due to LVEF dysfunction or any grade 4 toxicity.

A dose reduction below 30 mg BID is not allowed. Patients requiring additional reductions must be discontinued from study treatment. Dose interruptions of more than 21 days are not allowed.

**Recommended Dose Reductions for Binimetinib**

| | |
|---|---|
| First Dose Reduction | 30 mg orally twice daily |
| Subsequent Modification | Effectiveness of binimetinib at doses below 30 mg twice daily has not been demonstrated. |
| Dose Re-escalation | Patients who have been dose reduced to 30 mg twice daily may re-escalate to 45 mg twice daily if the AE that resulted in a dose reduction improved to baseline and remained stable for 14 days provided there were no other concomitant BINIMETINIB-related toxicities that would prevent drug re-escalation.<br><br>Do not re-escalate if the dose reduction is due to LVEF dysfunction or any grade 4 toxicity. |

Eye disorders should be graded according to CTCAE version 4.0 as described below in Table 1.

**Table 1 CTCAE grading for eye disorders**

| Grade | Description |
|---|---|
| 1 | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL |
| 3 | Severe or medically significant but not immediately sight threatening; Hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL |
| 4 | Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye |
| ADL= activities of daily living | |

Retinal detachment should be graded according to the CTCAE version 4.0 as described below in Table 2.

**Table 2 CTCAE grading for retinal detachment**

| Grade | Description |
|---|---|
| 1 | Asymptomatic |
| 2 | Exudative and visual acuity 20/40 or better |
| 3 | Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200) |
| 4 | Blindness (20/200 or worse) in the affected eye |

Uveitis should be graded according to the CTCAE version 4.0 as described below in Table 3.

**Table 3 CTCAE grading for uveitis**

| Grade | Description |
|---|---|
| 1 | Anterior uveitis; medical intervention indicated |
| 2 | Anterior uveitis; medical intervention indicated |
| 3 | Posterior or pan-uveitis |
| 4 | Blindness (20/200 or worse) in the affected eye |

Hand Foot Skin Reaction should be graded according to CTCAE version 4.0 as described below in Table 4.

**Table 4 CTCAE grading of Hand foot skin reaction (HFSR)[a]**

| Grade | Description[b] |
|---|---|
| 1 | Minimal skin changes or dermatitis (e.g., erythema, edema, numbness, dysesthesia, paresthesia, tingling or hyperkeratosis) without pain |
| 2 | Skin changes (e.g.,peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL |
| 3 | Severe skin changes (e.g., peeling, ulceration, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL |
| ADL=activities of daily living<br>[a]HFSR or palmar-plantar erythrodysaesthesia syndrome, a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet;<br>[b]More specifics examples to grade 1 and grade 3 are added to facilitate proper grading [from the sorafenib package insert (West Haven, CT: Bayer Pharmaceuticals Corporation; 2007); Porta et al 2007]. | |

Diarrhea should be graded according to CTCAE version 4.0 as described below in Table 5.

**Table 5 CTCAE grading of diarrhea**

| Grade | Description |
|---|---|
| 1 | Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline |
| 2 | Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline |
| 1-2 Complicated | Definition as above with the following complicating signs/symptoms:<br>• Moderate to severe cramping<br>• Grade ≥ 2 nausea/vomiting<br>• Decreased performance status<br>• Fever<br>• Sepsis<br>• Neutropenia<br>• Frank bleeding<br>• Dehydration<br>• Unresolved diarrhea after 48 hours of treatment with loperamide (including high dose administration) and initiation of second-line treatment |
| 3 | Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL |
| 4 | Life threatening consequences; urgent intervention indicated |
| ADL=activities of daily living | |

**Recommended Dose Reductions for Binimetinib**

| | |
|---|---|
| First Dose Reduction | 30 mg orally twice daily |
| Subsequent Modification | Effectiveness of binimetinib at doses below 30 mg twice daily has not been demonstrated. |
| Dose Re-escalation | Patients who have been dose reduced to 30 mg twice daily may re-escalate to 45 mg twice daily if the AE that resulted in a dose reduction improved to baseline and remained stable for 14 days provided there were no other concomitant BINIMETINIB-related toxicities that would prevent drug re-escalation.<br><br>Do not re-escalate if the dose reduction is due to LVEF dysfunction or any grade 4 toxicity. |

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Missed/skipped doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed). When the toxicity that resulted in a dose reduction improves to and remains stable at the patient's baseline for a minimum of 14 days, the dose can be re-escalated at the investigator's discretion provided there are no other concomitant toxicities.

No dose re-escalation is allowed after dose reduction due to left ventricular dysfunction or any grade 4 toxicity.

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below. All AEs should be followed weekly or as clinically appropriate until stabilization or resolution.

Please refer to the tables below for dose adjustment recommendations for binimetinib induced toxicities.

**Binimetinib – Recommended dose modifications associated with treatment-related adverse events**

| Severity of Adverse Reaction | BINIMETINIB |
|---|---|
| *Cutaneous Reactions* | |
| • Intolerable Grade 2 or 3<br>• Grade 4 | Withhold BINIMETINIB or reduce dose.<br>Permanently discontinue BINIMETINIB. |
| *Ocular* | |
| • Symptomatic Retinal pigment epithelial detachments | Withhold BINIMETINIB.<br>• If improved to Grade 0 or 1, resume at same dose level.<br>• If not improved, resume at the lower dose level or permanently discontinue. |
| • Retinal Vein Occlusion | Permanently discontinue BINIMETINIB. |
| *Cardiac* | |
| • Asymptomatic, absolute decrease of > 10% in LVEF compared to baseline and the LVEF is below the institutional lower limit of normal (LLN) (e.g., a decrease of 60% to 48% is an absolute decrease of 12%)<br><br>• Symptomatic congestive heart failure | Withhold BINIMETINIB for 3 weeks: repeat LVEF.<br><br>Resume BINIMETINIB at the lower dose level if all the following are present:<br>• LVEF at or above the LLN and<br>• Absolute decrease from baseline is 10% or less.<br>If the LVEF does not recover within 3 weeks, permanently discontinue treatment.<br><br>Permanently discontinue BINIMETINIB. |
| *Venous Thromboembolism* | |
| • Uncomplicated DVT or PE | Withhold BINIMETINIB for up to 3 weeks.<br>• If improved to Grade 0 or 1, resume at reduced dose.<br>• If not improved, permanently discontinue. |
| • Life threatening PE | Permanently discontinue BINIMETINIB. |
| *Liver Laboratory Abnormalities and Hepatotoxicity* | |
| • First occurrence Grade 4 | Withhold BINIMETINIB for up to 4 weeks.<br>• If improved to Grade 0 or 1, or Grade ≤2 if liver metastasis, then resume at reduced dose.<br>• If not improved to Grade 0 or 1 within 4 weeks, permanently discontinue. |
| • Recurrent Grade 4 | Permanently discontinue BINIMETINIB. |
| *Other* | |
| • Grade 2 (intolerable) adverse reactions | • Consider dose reduction, or<br>• Withhold BINIMETINIB for up to 3 weeks or until resolved to |

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| Severity of Adverse Reaction | BINIMETINIB |
|---|---|
| | Grade 0 or 1 and restart at a reduced dose. |
| • Grade 3 or 4 | Withhold BINIMETINIB for up to 3 weeks.<br>• If improved to Grade 0 or 1 or pretreatment/baseline level, resume at reduced dose.<br>• If not improved, permanently discontinue. |

a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0

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## SAFETY AND TOLERABILITY ASSESSMENTS

At every four-week visit (±3 days), the following assessments should be performed (until study drug discontinuation) for safety purposes: physical examination, 12-lead ECG, weight, vital signs, laboratory assessments (hematology, chemistry, CPK), and urinalysis.

- CPK will be performed at the same time points as the hematology collections. Follow up for total creatine kinase (CK) ≥ 3 X ULN will include weekly assessment of isoenzymes and myoglobin in blood/or urine, and troponin as applicable.

MUGA/echocardiogram will be performed to determine cardiac ejection fraction at the end of the second cycle, and then every four cycles thereafter. Whichever modality was used at baseline should be continued throughout the study.

Patients will undergo ophthalmology exams performed by an ophthalmologist during screening and at the end of the first cycle. Following the first cycle, patients will then undergo eye exams every 2 cycles or sooner if they become symptomatic. These will be full ophthalmic examinations including slit lamp examination, visual acuity testing, visual field testing, intraocular pressure (IOP) and indirect fundoscopy with attention to retinal abnormalities, especially retinal pigment epithelial detachments (RPED) like events and RVO.

For patients with clinical suspicion of retinal abnormalities (i.e. photopsia, metamorphopsia, impairment of visual acuity, etc.) or RVO, additional assessments of optical coherence tomography (for RPED) and fluorescein angiography (for RVO) should be **mandatory**.

## FOLLOW-UP FOR TOXICITIES

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as an ophthalmologist, cardiologist or dermatologist should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug-induced toxicities will be provided.

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### Monitoring of Hypertension

Patients that receive binimetinib must monitor their blood pressure at home at Days 10 and 30 after treatment initiation if they meet the following criteria:

- Patients with history of hypertension and/or

- Patient receiving antihypertensive drugs before onset of study treatment and/or
- Patients with a screening systolic blood pressure ≥ 140 mmHg and/or
- Patients with a screening diastolic blood pressure of ≥ 90 mmHg

The investigator is to educate the patient on the signs and symptoms of hypertension and use of the home blood pressure monitor. More frequent assessments during the study drug treatment period may also be performed at the discretion of the investigator and if medically indicated.

Measurements are to be taken at the same time on Study Days 10 and 30 after taking any hypertensive medications and after being at rest for 5 minutes in a sitting position. If SBP ≥160 mmHg, or DBP ≥ 100 mmHg, the patient should contact their investigator to have an unscheduled visit. At this unscheduled visit, the patient's blood pressure should be assessed and these measurements must be documented in the patient record. Early initiation of treatment and aggressive management of emergent hypertension must be implemented after its diagnosis.

For patients monitoring their blood pressure at home, it is suggested to develop a patient diary to record their self-assessed blood pressure measurements and present the collected data to the investigator for evaluation and appropriate management. This diary must be maintained in the patient's source documentation

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**Management of nausea and/or vomiting**

Because nausea and vomiting have been reported for binimetinib, it is recommended that patients are educated on the possibility of occurrence of these side effects prior to starting study treatment. Patient education as well as proper management of nausea and/or vomiting at the first sign is important. Clinical judgment and experience of the treating physician should guide the management plan of each patient. Patients experiencing nausea and/or vomiting CTCAE ≥ 1 will receive antiemetics at the discretion of the treating physician (as per local guideline). It is recommended that patients be provided a prescription for antiemetics, and are instructed on the use of antiemetics on the first day of study drug treatment. Prophylactic antiemetics such as dexamethasone 8 mg, prochlorperazine, or metoclopramide may be administered to patients on an "as needed" basis.

Dose interruption/reduction decisions for nausea and/or vomiting should be based on the CTCAE grade of the toxicity.

As a guidance for recommendations on supportive measures for the prevention and/or management of nausea and/or vomiting, the published recommendation from American Society of Clinical Oncology (ASCO), the European society of Medical Oncology (ESMO) and Multinational Association of supportive Care (MASCC) can be used (Basch et al, 2011; Roila et al 2010).

Recommended Guidelines for the Management of binimetinib-induced Diarrhea

**Proactively investigate for occurrence of diarrhea and educate patients**

1. Remind patients at each visit to contact the Investigator immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at each study visit, each patient should be asked regarding occurrence of diarrhea or diarrhea-related symptoms. If the patient had symptoms, the patient should

be asked regarding the actions taken for these symptoms and re-instruct if indicated

2. The patients should be instructed on dietary modifications and on early warning signs of diarrhea and potentially life-threatening illnesses (e.g. severe cramping might be a sign for severe diarrhea, fever with diarrhea might be a sign for infection, fever and dizziness on standing might be a sign for shock)
3. Patients should be educated about what to report to the Investigator (i.e., number of stools, stool composition, stool volume)

**Anti-diarrhea therapy**

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as outlined above as well as proper management of diarrhea is important.

Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. All concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications section of the patient record. It is recommended that patients be provided loperamide tablets and are instructed on the use of loperamide at on the first day of binimetinib treatment. In addition to the binimetinib induced-diarrhea dosing guidelines, these instructions should be provided at each visit and the site should ensure that the patient understands the instructions.

Explain the frequency of diarrhea and its relationship to NCI CTCAE grading.

Determine if diarrhea is complicated or uncomplicated.

**Rule out other or concomitant causes**

These may include:

- Infection with *Candida, Salmonella, Clostridium difficile, Campylobacter, Giardia, Entamoeba* and *Cryptosporidium species* can lead to severe infections in immunosuppressed patients
- Medication-induced diarrhea
- Malabsorption/lactose intolerance
- Fecal impaction, partial bowel obstruction

**For uncomplicated Grade 1/2 diarrhea**

- Stop all lactose-containing products, alcohol and eat frequent small meals that include bananas, rice, applesauce or toast)
- Stop laxatives, bulk fiber (i.e. Metamucil®) and stool softeners (e.g. docusate sodium; Colace®)
- Stop high-osmolar food supplements such as Ensure® Plus and Jevity® Plus (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade® or broth)
- Consider administration of standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Discontinue loperamide after 12-hours diarrhea-free (Grade 0) interval.

- If uncomplicated Grade 1 to 2 diarrhea persists for more than 24 hours, escalate to high dose loperamide: 2 mg every 2 hours (max. of 16 mg/day) or after each unformed stool.

**NOTE:** Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

- If uncomplicated Grade 1 to 2 diarrhea persists after 48 hours of treatment with loperamide, discontinue loperamide and begin a second-line agent which can be an opiate (opium tincture or paregoric), octreotide acetate or steroid (budesonide)

**For complicated Grade 1/2 diarrhea or any Grade 3 to 4 diarrhea**

- The patient must call the investigator immediately
- If loperamide has not been initiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Administer IV fluids and electrolytes as needed. In case of severe dehydration, replace loperamide by octreotide.
- Monitor/continue IV fluids and antibiotics as needed. Intervention should be continued until the patient is diarrhea free for at least 24 hours.
- Hospitalization may need to be considered.

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**Recommended Guidelines for the Management of Study Drug (binimetinib)-induced Skin Toxicity**

Clinical judgment and experience of the treating physician should guide the management plan of each patient:

- Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with study drug or later as needed
- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back

Topical agents include non-oily sunscreen (PABA free, SPF ≥ 30, UVA/UVB protection), topical steroids (preferably mometasone cream i.e. Elocon®) and topical erythromycin evening (i.e. Eryaknen® or topical pimocrolimus)

**NOTE:** Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to the first dose, and more often as needed.

- Possibly oral doxycycline (100 mg daily) for the first 2-3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

**Mild rash (CTCAE Grade 1)**

- Consider prophylactic rash treatment if not already started
- Topical or other topical corticosteroid (i.e. mometasone cream) and/or topical antibiotic (i.e. erythromycin 2%) are recommended.
- The patient should be reassessed within a maximum of 2 weeks or as per investigator opinion.

**Moderate rash (CTCAE Grade 2)**

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or pimecrolimus cream (1%) plus oral antibiotics such as: lymecycline (408 mg QD), doxycycline (100 mg BID) or minocycline (50 to 100 mg QD).
- Although there has been no evidence of phototoxicity or photosensitivity in patients being treated with binimetinib, doxycycline (or minocycline as second-line) should be used with thorough UV protection (i.e., avoidance of direct exposure to sunlight, use of sunscreen and sunglasses, etc.).
- Use of acitretin is not recommended

**Severe rash (CTCAE Grade 3-4)**

**CTCAE Grade 3**

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, i.e. 0.3 to 0.5 mg/kg) (Lacouture et al 2011)
- Use of acitretin is not recommended

**CTCAE Grade 4**

- Immediately discontinue the patient from study drug and treat the patient with oral and topical medications (see recommendation CTCAE Grade 3).

**Symptomatic treatment:**

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions, use cool compresses and oral antihistaminic agents
- For fissuring, use Monsel's solution, silver nitrate, or zinc oxide cream. If not sufficient use mild steroid ointments or combinations of steroids and antibiotics such as Fucicort®
- For desquamation, use emollients with mild pH 5/neutral (best containing urea 10%)
- For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and if no improvement is seen, refer to a dermatologist or surgeon
- For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

3.5 Supportive Care

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

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# 4. Study Parameters

## 4.1 Therapeutic Parameters for Binimetinib Treatment

**NOTE:** In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving binimetinib 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] |
|---|---|---|---|---|---|
| | | Every Cycle, prior to treatment | Every 2 Cycles | | |
| H&P, Weight, Vital signs[A] | X | X[I] | | | X |
| Performance status | X | X[I] | | | X |
| CBC w/diff, plts[B] | X | X[I] | | | X |
| Serum chemistry[B] | X | X[I] | | | X |
| Radiologic evaluation[D] | X | | X[D] | | X[F] |
| β-HCG[C] | X | | | | |
| Toxicity Assessment[G] | | X | | X | X[F] |
| Pill Count/Diary[H] | | X | | X | |
| Ophthalmologic examination | X | X[L] | X[L] | | |
| Echocardiogram or Nuclear Study[K] | X | | X[K] | | |
| Rev. Add13 ECG | X[J] | X[M] | | | |
| Rev. 3/17 Urinalysis | | X[M] | | | |
| Rev. 3/17 Tumor biopsy and blood sample for MATCH Master Protocol[E] | | | X | X[E] | |

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

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B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], creatine phosphokinase (CPK), 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. Please refer to Safety and Tolerability Assessments in Section 3.4 for additional assessments if CPK ≥3 X ULN.

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

Rev. Add13 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. 3/17, 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.

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. 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.

J. Within 8 weeks of treatment assignment.

K. Echocardiogram or MUGA scan will be done at the end of the second cycle, and then every four cycles thereafter.

L. Patients will undergo ophthalmology exams performed by an ophthalmologist during screening and at the end of the first cycle. Following the first cycle, patients will then undergo eye exams every 2 cycles or sooner if they become symptomatic. The ophthalmic exam should include slit lamp examination, visual acuity testing, visual field testing, intraocular pressure (IOP) and indirect fundoscopy with attention to retinal abnormalities, especially retinal pigment epithelial detachments (RPED) like events and retinal vein occlusion (RVO).

Rev. Add13 M. Please refer to Safety and Tolerability Assessments in Section 3.4 for additional information.

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## 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 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

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**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).

**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.

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**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 Binimetinib (NSC #788187)

### 5.1.1 Other Names

MEK162, ARRY-438162

### 5.1.2 Classification

MEK 1/2 inhibitor

### 5.1.3 Mode of Action

Binimetinib is a potent, selective, allosteric small-molecule inhibitor of mitogen-activated protein (MAP) kinase kinase (MEK 1 and MEK 2) that is uncompetitive with adenosine triphosphate (ATP).

### 5.1.4 Storage and Stability

**Storage:** Store below 25°C, protect from light

If a storage temperature excursion is identified, promptly return binimetinib to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

**Stability:** Stability studies are ongoing. Tablets should be dispensed in the original packaging.

### 5.1.5 Dose Specifics

Each patient will be treated with binimetinib 45mg twice daily continuously throughout the trial. Each dose of binimetinib should be taken with a glass of water (with or without food).

### 5.1.6 How Supplied

Array Biopharma supplies and CTEP, NCI, DCTD distributes binimetinib as 15 mg film-coated tablets in bottles containing 56 tablets. The capsule-shaped tablets are yellow to dark yellow and the size is 0.2 x 0.48 inches. The film-coated tablets consist of binimetinib drug substance; colloidal silicon dioxide; croscarmellose sodium; lactose monohydrate; magnesium stearate; microcrystalline cellulose; and a commercial film coating.

### 5.1.7 Route of Administration

Orally with or without food. Tablets should be swallowed whole.

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### 5.1.8 Incompatibilities

In vitro, binimetinib is metabolized primarily by glucuronidation mainly via UGT1A1 but also UGT1A3 and 1A9. Binimetinib is a substrate of CYP1A1, 1A2, 2C19, 3A4 in vitro but the potential for a clinical drug interaction is expected to be minimal. Binimetinib is also a substrate of P-gp and BCRP. Inhibitors or inducers of UGT1A1, P-gp, and BCRP should be co-administered with caution.

In vitro, binimetinib showed relatively potent inhibitory effect on CYP2B6 and weak inhibition of CYP1A2 and 2C9. Avoid co-administration with agents that are substrates of CYP2B6. It has little

or no inhibition of CYP2A6, 2C8, 2C19, 2D6, 2E1, and 3A4/5. Binimetinib is a weak inhibitor of UGT1A-mediated SN-38 conjugation in vitro. Binimetinib was not found to be an in vitro inhibitor of BCRP, P-gp, or OCT1 but is a weak inhibitor of OCT2. There is a low potential for binimetinib to cause a clinical drug interaction with substrates mainly cleared by OATP and OCT2.

Binimetinib is an in vitro inducer of CYP3A4 but this was not confirmed clinically. Slight induction of CYP2C9 mRNA was also found but did not translate into induction of activity.

Binimetinib is highly protein bound (97.2%). Use caution in patients who are receiving concomitant medications that are also highly protein-bound.

Drugs with a conditional, possible, or known risk to induce Torsades de Pointes or QT prolongation should be co-administered with caution. Patients that take these medications should be monitored frequently or according to protocol.

5.1.9 Side Effects

See Section 3.3 for side effects.

5.1.10 Patient Care Implications

There is some data that suggest binimetinib exposure may be associated with reproductive toxicity. Binimetinib must not be used in pregnant or nursing women.

## 6. Translational Studies

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

## 7. References

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# Molecular Analysis for Therapy Choice (MATCH)
# MATCH Treatment Subprotocol Z1A: Binimetinib/NRAS

## Appendix I

## Patient Pill Calendar

**Pill Calendar Directions**

1. Take your scheduled dose by mouth twice daily. Each dose should be taken approximately 12 hours apart.
2. Missed or vomited doses should not be replaced.
3. If you forget, the missed tablets will not be taken later.
4. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
5. Each dose of binimetinib should be taken with a glass of water (with or without food).
6. Binimetinib tablets should be swallowed whole.
7. Store binimetinib at room temperature.

## 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.

### Binimetinib

| DAY | Date | | | Time tablets taken | | Number of tablets taken | | Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.) |
|---|---|---|---|---|---|---|---|---|
| | Month | Day | Year | AM | PM | AM | PM | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | | | | | | | | |
| 10 | | | | | | | | |
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| 17 | | | | | | | | |
| 18 | | | | | | | | |
| 19 | | | | | | | | |
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Patient Signature: _____ Date: _____

# Molecular Analysis for Therapy Choice (MATCH)
# MATCH Treatment Subprotocol Z1A: Binimetinib/NRAS

## Appendix II

## Actionable Mutations for Sub-Protocol EAY131-Z1A

| Gene | Variant ID | Variant Description | Level of Evidence Code |
|---|---|---|---|
| NRAS | COSM585 | p.Q61H | 2 |
| NRAS | COSM586 | p.Q61H | 2 |
| NRAS | COSM583 | p.Q61L | 2 |
| NRAS | COSM584 | p.Q61R | 2 |
| NRAS | COSM582 | p.Q61P | 2 |
| NRAS | COSM581 | p.Q61E | 2 |
| NRAS | COSM580 | p.Q61K | 2 |
| NRAS | COSM574 | p.G13V | 3 |
| NRAS | COSM575 | p.G13A | 3 |
| NRAS | COSM573 | p.G13D | 3 |
| NRAS | COSM570 | p.G13C | 3 |
| NRAS | COSM569 | p.G13R | 3 |
| NRAS | COSM571 | p.G13S | 3 |
| NRAS | COSM566 | p.G12V | 2 |
| NRAS | COSM565 | p.G12A | 3 |
| NRAS | COSM564 | p.G12D | 2 |
| NRAS | COSM562 | p.G12C | 3 |
| NRAS | COSM561 | p.G12R | 3 |
| NRAS | COSM563 | p.G12S | 3 |

**Molecular Analysis for Therapy Choice (MATCH)**
**MATCH Treatment Subprotocol Z1A: Binimetinib/NRAS**

## Appendix III

## Patient Drug Information Handout and Wallet Card

### Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **binimetinib**. 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.

### These are the things that you as a healthcare provider need to know:

**Binimetinib** interacts with certain specific enzymes in your liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are **UGT1A1 and CYP 2B6**. Binimetinib is broken down by UGT1A1 and may be affected by other drugs that inhibit or induce this enzyme. Binimetinib is a strong inhibitor of CYP 2B6 and may affect other drugs that are broken down by this enzyme.
- The transport proteins in question are **P-gp and BCRP**. Binimetinib is moved in and out of cells/organs by these transport proteins and may be affected by inhibitors or inducers of P-gp and BCRP.
- Binimetinib is highly protein bound (97.2%). Patients receiving other medications that are also highly protein bound may need to be monitored more frequently.
- Drugs that are known to or may cause Torsades de Pointes or prolong QT interval should be used with caution. Patients taking these medications should be monitored frequently.

### To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

**Binimetinib** may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

### These are the things that you and they need to know:

**Binimetinib** must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of UGT1A1,

inhibitors and inducers of P-gp and BCRP. Binimetinib inhibits CYP 2B6 and may change how other medicines work in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- You may need to be monitored more frequently if you are receiving other medications that are also highly protein bound, are known to or may cause Torsades de Pointes, or prolong QT interval.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

Your study doctor's name is

_____

and he or she can be contacted at:

_____.

**STUDY DRUG INFORMATION WALLET CARD**

You are enrolled on a clinical trial using the experimental study drug binimetinib. This clinical trial is sponsored by the NCI. Binimetinib may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) 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.
- You may need to be monitored more frequently if you are receiving other medications that are also highly protein bound, are known to or may cause Torsades de Pointes, or prolong QT interval.

**Binimetinib** interacts with **specific liver enzymes called UGT1A1, CYP 2B6, and transport proteins P-gp and BCRP**, and must be used very carefully with other medicines that interact with these enzymes and transporters.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of UGT1A1, or inhibitors and inducers of transporters P-gp and BCRP. Binimetinib inhibits CYP 2B6 and may change how other medicines work in your body."**
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated 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 _____.