August 19, 2020

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

Dear Ms. Kruhm:

Enclosed is Addendum #25 to EAY131-C1, *Crizotinib in Patients with Tumors with MET Amplification*

This addendum is in response to Dr. Tali Johnson's Amendment Request for updates to specific protocol language for Crizotinib dated June 5, 2020.

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

IRB Review Requirements:

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

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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

Re: Review of Amendment #36 of Protocol #EAY131-C1: "MATCH Treatment Subprotocol C1: Crizotinib in Patients with Tumors with MET Amplification". The following are ECOG-ACRIN's responses to the CTEP review comments dated 5/26/2020. Please note that the Principal Investigator's comments appear in bold below.

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	***ICD*- Why is this study being done?**	Under **Why is this study being done?** on page 1, please change the target accrual back to 50, consistent with protocol amendment #35: There will be about 35 50 people taking part in this study. **PI Response: This has been corrected.**

II. Additional Protocol Changes by Principal Investigator:

The following revisions to EAY131-C1 protocol have been made in this addendum:

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	Section	Change
1.	Cover Page	Updated Version Date and addendum number.
2.	Cover Page	In second note, removed language in second sentence referencing an activation memo.
3.	3.2.1	Revised language in the second box referencing “subject’ to “female patient”
4.	Appendix III	Updated patient drug information template format.

The following revisions to EAY131-C1 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.

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

We request review and approval of this addendum to EAY131-C1 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol C1: Crizotinib in Patients with Tumors with MET Amplification

CRIZOTINIB TREATMENT SUBPROTOCOL CHAIR: David S. Hong, MD
CRIZOTINIB TRANSLATIONAL CHAIR: Daniel Catenacci, MD

Version Date: August 19, 2020

NOTE: This subprotocol (EAY131-C1) 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.**

Rev. Add25

SUBPROTOCOL ACTIVATION DATE

May 31, 2016 (Incorporated in Addendum #3)
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #11 – 8/17
Addendum #13
Addendum #18
Addendum #24
Addendum #25

Agent	IND#	NSC#	Supply
Crizotinib	IND Sponsor: DCTD, NCI IND#: [redacted]	749005	NCI Supplied

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Schema

Cycle = 28 days
Accrual Goal: 50

1. Introduction

1.1 Crizotinib

1.1.1 Background

Deregulated signaling by the epithelial cell receptor tyrosine kinase (RTK), MET, appears critical to the growth, invasion, and metastasis of many solid tumors. Under physiological conditions, MET and its ligand, hepatocyte growth factor (HGF), regulate pathways essential for embryogenesis, liver regeneration and wound healing. HGF initiates these pathways by inducing MET dimerization and autophosphorylation which activates signaling cascades that promote cell proliferation, migration, matrix invasion and branching morphogenesis (Birchmeier et al., 2003; Comoglio et al., 2008; Naran et al., 2009) HGF can also drive aberrant MET signaling in cancer through autocrine loops(Catenacci et al., 2011); however, MET activation also occurs independently of HGF via gene amplification and consequent MET over-expression (Smolen et al., 2006) as well as, more rarely, mutation and/or cross-talk with RTKs and other receptors.

Over-expression of MET has been observed in most solid tumors and correlates with poor prognosis (Birchmeier et al., 2003; Comoglio et al., 2008; Graziano et al., 2011; Naran et al., 2009). MET over-expression via gene amplification occurs in glioblastoma (< 5%), gastric cancer (4-< 5%), and colorectal cancer (< 3%). MET amplification also occurs in lung cancer subjects resistant to EGFR inhibitors, where it appears to mediate drug resistance (Engelman et al., 2007). Germ-line gain-of-function MET mutations commonly occur in hereditary papillary renal cancer, and somatic activating MET mutations have been reported in head and neck cancer, sporadic papillary renal cancer, non Hodgkin's lymphoma, and rarely in ovarian and lung cancer. (Johnson et al. 2012)

However, the story of MET in all cancers is not entirely clear. For example onartuzumab, an antibody that targets the MET receptor, combined with erlotinib, showed improved progression free and overall survival in the MET positive (assessed by IHC) lung cancer population in a phase II trial, but failed to show a difference in progression free or overall survival in a large randomized phase 3 trial of onartuzumab in combination to erlotinib compared to erlotinib alone in non-small lung cancer (median 2.7 versus 2.6 months, P=0.92). Moreover the overall survival trended in favor of erlotinib alone (9.1 months vs 6.8 on the combination m p=0.07). (Spigel et al, ASCO 2014).

Likewise, in the Phase III Multinational, Randomized, Double-Blind, Placebo-Controlled Study of Tivantinib (ARQ 197) Plus Erlotinib Versus Erlotinib Alone in Previously Treated Patients With Locally Advanced or Metastatic Nonsquamous Non–Small-Cell Lung Cancer Scagliotti et al (2015) reported that the study was ended early for futility and did not improve overall survival. However, in a preplanned

subgroup exploratory analysis, of 211 patients with high MET expression by IHC, the combination of erlotinib and tivantinib had improved median overall survival (9.3 vs 5.9 months).

The reasons for failure of these trials in NSCLC is not fully understood, but may be due to differences in how MET amplification or overexpression were measured. Others have shown that MET maybe a valid target in MET amplified NSCLC. For example, D. Ross Camidge showed that durable responses were seen in MET high amplified NSCLC patients treated with criztoinib (D. Ross Camidge et al, ASCO 2014).

Collectively, however, the data indicate that MET plays a broad and supporting role in oncogenesis and drug resistance and that MET is a valid target for cancer therapy.

Crizotinib is an inhibitor of the MET, ALK, and ROS1 receptor tyrosine kinases that was recently approved by the Food and Drug Administration for treatment of ALK-positive non-small cell lung cancer (NSCLC) because of a striking response rate in those tested positive for ALK rearrangement. ALK rearrangement can also be found in a subset of patients with sarcoma, breast cancer, and lymphoma, but their response to this agent is as of yet unknown. Recently, Crizotinib also was FDA approved to treat ROS1 positive tumors because it was shown to be highly active in the treatment of lung cancer harboring ROS1 gene rearrangement (Shaw, et al., 2012 and its activity as a MET inhibitor in tumors with MET amplification is considerable(Tanizaki, et al, 2011; Ou et al., 2011). Despite a proven efficacy in these genetic subsets of cancers, acquired or intrinsic resistance is common and leads to tumor progression, highlighting the need to combine this drug with other agents.

Crizotinib is an oral small-molecule inhibitor of ALK, MET, and ROS1 receptor tyrosine kinases. It was first discovered through a screen of inhibitors of MET, the receptor for HGF. The kinase selectivity of crizotinib was evaluated against a panel of more than 120 human kinases; crizotinib inhibited autophosphorylation of both MET and ALK with high potency and specificity (Cui et al, 2011).

Crizotinib demonstrated concentration-dependent inhibition of ALK and MET phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed EML4- or NPM-ALK fusion proteins or MET.

The IC_{50} of crizotinib in blocking MET phosphorylation and MET dependent cell growth and invasion in a variety of cell lines is 5-20 nM (Cui et al, 2011). Crizotinib blocks cell proliferation and enhances apoptosis in NSCLC lines carrying an EML4-ALK fusion in the range of 250-340 nM. Based upon clinical pharmacokinetic data, more than 70% of ALK inhibition is projected at the FDA-approved dose of 250 mg twice a day and, thus, a highly MET inhibition is also expected at this dose (Gandhi et al., 2012).

Administration of crizotinib at pharmacologic doses to MET amplified cell lines results in marked inhibition of phosphorylated MET, Akt, Erk,

STAT5 and PLCλ1 levels (Zou et al., 2007). A significant dose dependent reduction of human VEGFA and IL-8 plasma levels in Met positive tumor-bearing mice was also observed. In addition, crizotinib potently inhibits HGF-stimulated endothelial cell survival and invasion (Cui et al, 2011). These results suggest that antitumor activity of crizotinib may be mediated by direct effects upon pivotal pathways in cancer cells as well as an antiangiogenic effect. Its activity as a MET inhibitor in tumors with MET amplification is considerable(Tanizaki, et al, 2011; Ou et al., 2011).

1.2 Supporting Preliminary Data

1.2.1 Crizotinib Preclinical Pharmacology and Efficacy

In the preclinical setting, crizotinib blocks MET activation across multiple tumor types. Data were generated in gastric and breast carcinoma cells, prostate, squamous head and neck cancer, osteosarcoma, ovarian cancer and renal cancer (Zou et al., 2007). Convincing pre-clinical evidence for induction of apoptosis by crizotinib in gastric cancer cells with MET amplification has been published (Sampson et al, 2011). Crizotinib also showed in the lab to induce cell death in head and neck cancer when combined with dasatinib in cells that were previously resistant to this drug (Sen et al, 2011).

1.2.2 Summary of Clinical Experience

Crizotinib is approved for use in patients with advanced NSCLC who have evidence of anaplastic lymphoma kinase (ALK)-positive tumor as detected by the FDA approved test for the EML4-ALK gene fusion. This alteration is observed in about 5% of patients with NSCLC. The response rates seen in early-phase studies in ALK-positive NSCLC led to the accelerated FDA approval of crizotinib in this setting (Kwak et al., 2010). In addition to ALK inhibition in NSCLC, there is clinical evidence of efficacy of crizotinib in NSCLC harboring ROS1 rearrangements and in inflammatory myofibroblastic tumor (IMT) and anaplastic large-cell lymphoma (ALCL) with ALK aberrations. Moreover, crizotinib has shown clinical efficacy in MET amplified NSCLC, esophagogastric adenocarcinoma and glioblastoma.

In a patient with advanced NSCLC whose tumor was identified as harboring de-novo MET amplification but no ALK rearrangement by FISH (Ou et al., 2011), treatment with crizotinib resulted in rapid tumor shrinkage and partial response. This validated MET amplification as a molecular driver that could be therapeutically targeted with MET inhibitors. Lennerz et al. reported 2 cases of MET-amplified esophagogastric cancers which exhibited tumor shrinkage in response to crizotinib, again supporting a role for MET inhibitor therapy in MET-amplified tumors (Lennerz et al, 2011). Furthermore, a case report of a patient with a -MET amplified glioblastoma described a rapid clinical improvement and a 40% reduction in the central lesion while receiving crizotinib (Chi et al, 2011). Progression was detected after 6 months of crizotinib initiation.

Pharmacokinetics

Absorption

The Phase I trial of crizotinib showed that patients treated at the recommended phase 2 dose (RP2D) were noted to achieve a Cmax of the drug at a median Tmax of 4 hours with a terminal half-life of 42 hours following a single oral dose. Steady-state levels were reached within 15 days, with a non-linear pharmacokinetics as reflected by decreases in CL/F observed with multiple doses. Steady state systemic exposure (Cmin and AUC) appeared to increase in a greater than dose proportional manner over the dose range of 200-300 mg twice daily.

The mean absolute bioavailability of crizotinib was 43% (range: 32% to 66%) following the administration of a single 250 mg oral dose. A high-fat meal reduced crizotinib AUC and Cmax by approximately 14%. A mouse model showed that the EC_{50} for ALK inhibition approximately corresponded to the EC_{50} for tumor growth inhibition, suggesting that >50% of ALK inhibition would be required for tumor killing of >50%. Based in a non clinical mouse xenograft model more than 70% of ALK inhibition is projected in lung cancer patients taking the usual dose of crizotinib, 250 mg twice daily.

Distribution

The geometric mean volume of distribution (Vss) of crizotinib was 1,772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma. Binding of crizotinib to human plasma proteins *in vitro* is 91% and is independent of drug concentration. *In vitro* studies suggested that crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately 1.

Metabolism

In vitro studies demonstrated that crizotinib is predominantly metabolized by CYP3A4/5 (package insert). Additional information is found in Section 5.1.8. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and *O*-dealkylation, with subsequent Phase 2 conjugation of *O*-dealkylated metabolites. *In vitro* studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A.

Elimination

Following single doses of crizotinib, the mean apparent plasma terminal half-life of crizotinib was 42 hours in patients. Following the administration of a single 250 mg radiolabeled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in feces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in feces and urine, respectively.

The mean apparent clearance (CL/F) of crizotinib was lower at steady state (60 L/hr) after 250 mg twice daily than that after a single

250 mg oral dose (100 L/hr), which was likely due to autoinhibition of CYP3A by crizotinib after multiple dosing.

Rev. Add24

1.3 MET Amplification Criteria

It is known that the degree of increase of MET gene copy number (GCN) correlates with prognosis in various tumor types (Cappuzzo et al., 2009; Graziano et al., 2011) and also the degree of MET protein over-expression (Catenacci et al., 2014). The degree of amplification also correlates with response to MET TKIs (Lennerz et al., 2011; Smolen et al., 2006). Therefore, eligibility for the crizotinib subprotocol of the NCI-MATCH trial will require a minimum elevation of gene copy number of ≥7 copies/cell as assessed by the central Oncomine® Assay which will be ≥15 copies per cell for those Designated Laboratories that correct for tumor content.

1.4 Arm Expansion

1.4.1 In some circumstances, it may necessary to expand a treatment arm if an inadequate number of assays from Designated Laboratories can be confirmed by the central Oncomine® Assay to ensure 31 evaluable patients for the primary endpoint. In those circumstances, the study will be expanded to achieve a total of 35 patients, i.e. the number of cases to allow for attrition so that at least 31 patients are evaluable for the primary endpoint.

1.4.2 After the first 35 patients was enrolled on the trial it was suspended per protocol guidelines and assessement of confirmation was performed. It was determined that only 4 cases were confirmed by the central Oncomine® Assay and, when added to the 13 patients that were originally assessed by the Oncomine® Assay, that indicated that only 17 patients could be considered evaluable for the primary endpoint. Hence, it was decided that an additional 15 patients should be accrued for a total of 50 patients to allow a total of 35 patients as per guidelines above. In addition, a cut-off of ≥15 copies per cell was set for Designated Laboratories that correct for tumor content as a post-hoc evaluation of concordance across treatment arms with amplification requirements revealed that these laboratories were overcalling copy number as defined by the Oncomine® Assay (see Section 1.3 and 2.1.2). If planned accrual is not completed within 21 months, the expansion cohort will be closed to further accrual.

2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the main screening study, 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: All CTEP 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 a relevant treatment consent form

2.1 Registration to Treatment

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

Rev. Add13
Rev. Add24

_____ 2.1.2 Patient must have MET amplification as defined via the MATCH Master Protocol and described in Appendix V. Amplified MET will be defined as ≥ 7 copies/cell as identified by the Oncomine® Assay, or the Oncomine® Assay equivalent of 7 or greater as identified by a Designated Laboratory assay which will be ≥15 copies per cell for those Designated Laboratories that correct for tumor content. See Appendix V for information on the MET mutations and corresponding Levels of Evidence.

_____ 2.1.3 Patients must have an electrocardigram (ECG) within 8 weeks prior to treatment assignment and must not have clinically important abnormalities in rhythm, conduction or morphology of resting ECG, including complete left bundle branch block, third degree heart block.

Date of ECG: _____

_____ 2.1.4 Patients must not have known hypersensitivity to crizotinib or compounds of similar chemical or biologic composition.

Date: _____

_____ 2.1.5 Patient must not have had any of the following prior therapies: AMG 337, BMS 777607, Cabozantinib (XL184), Crizotinib (PF02341066), EMD1214063, Foretinib (GSK1363089) (XL880), Golvatinib (E7050), IncB28060 (INC280), JNJ 8877605, MGCD265, MK2461, MSC2156119J, PF 04217903, SGX523, Tivantinib (ARQ197) or any other novel MET TKI with any MET inhibitory activity IC50 < 1 uM. Prior anti-HGF or anti-MET antibodies are acceptable.

_____ 2.1.6 Patients must not have a history of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.

_____ 2.1.7 Patients must not have had myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischemic attack within 3 months prior to start of study treatment * Clinically significant GI abnormalities that may alter absorption (e.g., malabsorption syndrome, major resection of stomach or small bowel).

_____ 2.1.8 Patients using drugs or foods that are known strong CYP3A4 inhibitors or inducers will be excluded. Patients must not require concurrent use of CYP3A substrates with narrow therapeutic indices. Please see Appendix II.

_____ 2.1.9 Patients must not have had major surgery or tumor embolization within 4 weeks and minor surgery within 2 weeks prior to the initiation of the study drug.

_____ _____

Physician Signature Date

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

3. Crizotinib Treatment Plan

3.1 Administration Schedule

Study Drug: Crizotinib

Crizotinib capsules, 250 mg, will be administered orally twice daily on a continuous daily dosing schedule. Crizotinib should be taken approximately 12 hours apart and without regard to meals. Cycles are defined in 28-day periods to facilitate scheduling of visits and assessments.

Rev. 3/17

Patients should be instructed that if they vomit after taking a dose, then they must not "make it up" with an extra dose, but instead, resume subsequent doses as prescribed. Capsules should not be crushed. Any missed dose may be taken up to 6 hours prior to the next schedule dose, otherwise it should be skipped and dosing resumed with subsequent doses.

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 instructions for protocol EAY131 – Subprotocol C1

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.

Rev. Add25

EAY131-C1 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 female patient is on crizotinib, or within 28 days of the female patient's last dose of crizotinib, 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 screening protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131-C1 specific expedited reporting exceptions:

For study Subprotocol C1, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

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

3.2.2 Second Primary Cancer Reporting Requirements

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

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

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

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

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

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

Rev. 8/17
Rev. Add18

3.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Crizotinib (PF-02341066, NSC 749005)

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 2058 patients.* Below is the CAEPR for Crizotinib (PF-02341066).

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 2.3, October 30, 2018[1]

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			**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)***
		Febrile neutropenia	
CARDIAC DISORDERS			
		Heart failure	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
		Testosterone deficiency	
EYE DISORDERS			
Eye disorders - Other (vision disorders)[2]			***Eye disorders - Other (vision disorders)[2] (Gr 2)***
Periorbital edema			***Periorbital edema (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colonic perforation	
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
		Esophageal ulcer	
		Esophagitis	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema face			***Edema face (Gr 2)***

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Generalized edema			***Generalized edema (Gr 2)***
Localized edema			***Localized edema (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (hepatotoxicity)	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
		Blood bilirubin increased	
	Creatinine increased		
		Electrocardiogram QT corrected interval prolonged	
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		
	Nervous system disorders - Other (neuropathy)[3]		***Nervous system disorders - Other (neuropathy)[3] (Gr 2)***
		Syncope	

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (renal cyst)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[4]		

[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]Vision disorders may include the following: Chromatopsia, Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Vitreous floaters, and Visual perseveration.

[3]Neuropathy may include the following: Acute polyneuropathy, Amyotrophy, Areflexia, Autoimmune neuropathy, Autonomic failure syndrome, Autonomic neuropathy, Axonal neuropathy, Biopsy peripheral nerve abnormal, Burning feet syndrome, Burning sensation, Decreased vibratory sense, Demyelinating polyneuropathy, Dysesthesia, Electromyogram abnormal, Formication, Gait disturbance, Genital hypoesthesia, Guillain-Barre syndrome, Hyperesthesia, Hypoesthesia, Hyporeflexia, Hypotonia, Ischemic neuropathy, Loss of proprioception, Miller Fisher syndrome, Mononeuritis, Mononeuropathy, Mononeuropathy multiplex, Motor dysfunction, Multifocal motor neuropathy, Muscle atrophy, Muscular weakness, Myelopathy, Nerve conduction studies abnormal, Nerve degeneration, Neuralgia, Neuritis, Neuromuscular toxicity, Neuromyopathy, Neuropathy peripheral, Neuropathy vitamin B6 deficiency, Neurotoxicity, Paresthesia, Peripheral motor neuropathy, Peripheral nerve lesion, Peripheral nerve palsy, Peripheral nervous system function test abnormal, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal muscular atrophy, Peroneal nerve palsy, Phrenic nerve paralysis, Polyneuropathy, Polyneuropathy chronic, Polyneuropathy idiopathic progressive, Radiation neuropathy, Sensorimotor disorder, Sensory disturbance, Sensory loss, Skin burning sensation, Temperature perception test decreased, Tinel's sign, Toxic neuropathy, and Ulnar neuritis.

[4]Treatment-related rash may include erythematous rash, rash maculo-papular, and pruritus.

Adverse events reported on crizotinib (PF-02341066) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that crizotinib (PF-02341066) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (basophilia); Disseminated intravascular coagulation; Eosinophilia; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Myocarditis; Pericardial effusion; Supraventricular tachycardia

EYE DISORDERS - Cataract; Optic nerve disorder; Papilledema

GASTROINTESTINAL DISORDERS - Colitis; Dysphagia; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal amyloidosis); Ileus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; General disorders and administration site conditions - Other (failure to thrive); Malaise; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatitis)

IMMUNE SYSTEM DISORDERS - Autoimmune disorder

INFECTIONS AND INFESTATIONS - Abdominal infection; Infections and infestations - Other (peridiverticular abscess); Kidney infection; Lung infection; Sepsis; Skin infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (traumatic lung injury); Spinal fracture; Wound complication

INVESTIGATIONS - Blood lactate dehydrogenase increased; CPK increased; GGT increased; Investigations - Other (monocyte count increased); Investigations - Other (platelet count increased); Platelet count decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Musculoskeletal and connective tissue disorder - Other (myopathy); Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor hemorrhage

NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Ischemia cerebrovascular; Pyramidal tract syndrome; Seizure; Stroke

PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS - Pregnancy loss

PSYCHIATRIC DISORDERS - Confusion; Delirium; Euphoria

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Renal calculi; Urinary retention

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Dyspnea; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (drug eruption)

VASCULAR DISORDERS - Hematoma; Hypotension; Phlebitis; Thromboembolic event; Vasculitis

NOTE: Crizotinib (PF-02341066) 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).

Patients will be monitored closely for toxicity and the dose of crizotinib may be adjusted as indicated in Table 3.5. Intrapatient dose reduction by 1, and if needed, 2 dose level(s) will be allowed depending on the type and severity of toxicity encountered.

Dose Level	Crizotinib Dose
1	250mg BID
-1	200mg BID
-2	250mg Daily

Patients requiring more than 2 dose reductions due to treatment-toxicity will be removed from treatment. Patients requiring treatment to be held for >4 weeks will be taken off treatment.

Table 3.5 Crizotinib Dose Modifications for Treatment-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non- hematologic General (except as noted below), eg, neuropathy, edema (including peripheral edema and localized edema), fatigue, and skin rash (including erythematous, macular, papular, and pruritic rash)	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 resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.*	Withhold dose until toxicity is Grade ≤ 1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator*.
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade ≤1 total bilirubin	Continue at the same dose level.	Continue at the same dose level. Obtain repeat ALT and total bilirubin when symptomatic or within 7 days.	Withhold until recovery to Grade ≤1 or baseline, then resume at 200 mg twice daily. In case of recurrence, withhold until recovery to Grade ≤1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.	See Grade 3.
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or hemolysis)	Continue at the same dose level. Obtain repeat ALT and total bilirubin within 48 hours.	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat
Left ventricular systolic dysfunction	Continue at the same dose level	Continue at the same dose level	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat
Prolonged QTc	Continue at the same dose level	Assess electrolytes and concomitant medications. Correct any electrolyte or magnesium abnormalities	Withhold until recovery to Grade ≤1, then resume at 200 mg twice daily In case of recurrence, withhold until recovery to Grade ≤1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.	Discontinue treatment and do not retreat
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat	Discontinue treatment and do not retreat
Visual disturbance	Continue at the same dose level. Repeat ophthalmologic examination+	Continue at the same dose level. Repeat ophthalmologic examination+	Interrupt crizotinib until recovery. Repeat ophthalmologic examination+. Resume treatment by reducing by one dose level.	Discontinue treatment and do not retreat. Repeat ophthalmologic examination+.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic (excluding lymphopenia**)	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤ 2, or has returned to baseline, then resume treatment at the same dose level or reduce by 1 level after discussion with the study chair**/***.	Withhold dose until toxicity is Grade ≤ 2, or has returned to baseline, then reduce the dose by 1 level and resume treatment**.
Hypophosphatemia or hyperuricemia*	Continue at the same dose level	Continue at the same dose level	Continue at the same dose level at investigator discretion	Discontinue treatment until resolution to grade 3 or lower

* Patients who develop Grade 3 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification.

** Patients who develop Grade 3 or 4 lymphopenia without other dose-limiting events (eg, opportunistic infection) may continue study treatment without interruption.

*** Patients entering with platelet counts > 30,000 (to < 50,000/μL) will be monitored for drug related decreases at which point dose modifications will be discussed with the Sponsor

§ Patients entering with ALT and/or AST ≥ 5 x ULN (ie, Grade ≥ 3) due to underlying malignancy will be monitored for potential drug related increases at which point dose modifications will be discussed with the Sponsor (Note: this option does not apply for France).

\+ Ophthalmologic examination includes visual acuity and slit lamp and should be performed by an ophthalmologist.

3.4.1 Missed Doses

A missed dose will not be made up. In the event that a subject requires an unscheduled interruption of crizotinib under conditions other than those associated with toxicity, the case will be reviewed by the Study Chair to determine whether such a subject will be allowed to resume crizotinib treatment.

3.5 Supportive Care

Throughout the duration of the study, all herbal supplements, vitamins, and nutritional supplements taken must be reviewed and approved by the Investigator prior to administration.

3.5.1 Nausea and emesis: For nausea and vomiting, treat with standard anti-emetics such as prochloroperazine or ondansetron. Patients should be counseled that taking the medication with food may reduce nausea. The use of prophylactic antiemetics should be considered. Given the potential for ondansetron to increase QTc prolongation, review baseline QTc EKG prior to initiation of ondansetron and consider follow up EKGs on treatment.

3.5.2 Diarrhea: For grade 1 diarrhea, symptomatic care such as loperamide (Imodium) or no intervention at investigator judgment. For grade 2 diarrhea, loperamide (4 mg at first onset, then 2 mg every 2-4 hrs until symptom free for 12 hours). See Table 3.5.for instructions on dose modifications.

3.5.3 Bradycardia:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Bradycardia (heart rate less than 60 beats per minute)	Continue at the same dose level.	Withhold until recovery to Grade ≤ 1 or to heart rate ≥ 60. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤ 1 or to heart rate ≥ 60. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤ 1 or to heart rate ≥60.	Same as for Grade 2 bradycardia.	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤ 1 or to heart rate ≥ 60, with frequent monitoring. Permanently discontinue for recurrence.

3.5.4 Pneumonitis/pneumonia: Investigators must evaluate thoroughly patients who demonstrate potential signs or symptoms of pneumonitis or pneumonia. If a patient has a potential diagnosis of pneumonitis or drug-related lung injury, the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis:

- Evaluate for pneumonia: Pneumonia would be supported by clinical symptoms/signs of infection, including fever, leukocytosis, productive cough, characteristic radiologic findings, and most importantly, documentation of microbiology studies (sputum gram/stain and culture, blood cultures). Pneumonia should be treated with the appropriate antibiotics and supportive care. Many of these symptoms/signs may be seen in pneumonitis, but in this case, all microbiological studies would be negative (including possibly bronchoscopy for specimens).
- Sputum gram stain and culture (induced sputum if needed), to evaluate for bacterial, viral, fungal, protozoal, and mycobacterial infections
- Blood cultures if febrile
- Thoracentesis if pleural fluid is present (examined for the same pathogens as in 3.6.4.1)
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. BAL fluid should be sent for culture and cytology
- Lung biopsy if appropriate and necessary to distinguish between pneumonia and pneumonitis
- BNP levels to evaluate for heart failure
- If clinically appropriate, particularly if pneumonia can be ruled out, high dose corticosteroid treatment should be initiated. Should the event be fatal, an autopsy is recommended to confirm/exclude the diagnosis.

3.5.5 Renal cysts: Complex renal cysts have been reported in some patients treated with crizotinib. These cysts may be symptomatic or asymptomatic, and typically develop between 2 and 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear. However, complex renal cysts can be associated with renal malignancy, so consultation with a urologist is recommended. Urinalysis should be performed if renal cysts are detected, and followed on Day 1 of each cycle thereafter. Urine reflex microscopy is required if the urinalysis demonstrates blood or protein.

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3.5.6 Hypogonadism: For males reporting symptoms of hypogonadism (fatigue, sexual dysfunction, decreased libido, mood or sleep disorder, gynecomastia), a panel of blood tests should be drawn, including total testosterone, free testosterone, and sex-hormone binding globulin (SHBG). If free testosterone is low, consultation with endocrinology is recommended for possible testosterone supplementation.

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

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4.1 Therapeutic Parameters for Crizotinib Treatment

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NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving crizotinib 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[J]			X
Performance status	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[F]
Pill Count/Diary[H]		X		X	
ECG[K]	X	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). Particular attention should be given to any signs of pulmonary fibrosis (shortness of breath, cough); these symptoms should be pursued with appropriate tests. Patients should be instructed to notify their provider if they have increased shortness of breath or cough.

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.

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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 arm 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

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.

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

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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 Crizotinib (NSC #749005)

5.1.1 Other Names

Xalkori®, PF-02341066

5.1.2 Classification

MET inhibitor

5.1.3 Mode of Action

Crizotinib is a selective ATP-competitive small –molecule inhibitor of anaplastic lymphoma kinase (ALK), MET/hepatocyte growth factor receptor (HGFR) and Recepteur d'Origine Nantais (RON), and ROS1 receptor tyrosine kinases and their oncogenic variants. Translocations of these genes can result in expression of oncogenic fusion proteins that contribute to increased cell proliferation and survival. Antitumor efficacy of crizotinib is correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion variants or MET /HGFR in tumors *in vivo*.

5.1.4 Storage and Stability

Storage: Store at room temperature 20° to 25° C (68° to 77° F).

Stability: Shelf life is consistent with commercially-labeled product.

5.1.5 Dose Specifics

Crizotinib capsules, 250 mg, will be administered orally twice daily on a continuous daily dosing schedule.

See Section 3.4 for dose modifications.

5.1.6 Preparation

Pfizer supplies and PMB, CTEP, DCTD distributes commercially-labeled crizotinib as 200 mg (size 1, white opaque body and pink opaque cap, with "Pfizer" on the cap and "CRZ 200" on the body) and 250 mg (size 0, pink opaque body and cap, with "Pfizer" on the cap and "CRZ 250 on the body) hard gelatin capsules. Each bottle contains 60 capsules.

Excipients include colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells as inactive ingredients.

The pink opaque capsule shell components contain gelatin, titanium dioxide, and red iron oxide. The white opaque capsule shell components contain gelatin, and titanium dioxide. The printing ink contains shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

5.1.7 Route of Administration

Oral. Take with or without food.

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5.1.8 Potential drug-interactions

Crizotinib is primarily metabolized by CYP 3A4/5 with minor contributions from CYP2C8, CYP2C19, and CYP2D6. Avoid concomitant use of strong CYP3A inhibitors and inducers. Use of potent CYP3A inducers should be avoided for at least 12 days prior to the first dose of crizotinib. Use of strong CYP3A inhibitors should be avoided for at least 7 days prior to the first dose of crizotinib. Exercise caution with concomitant use of moderate CYP3A inhibitors. Crizotinib moderately inhibits CYP3A4 in a time-dependent fashion. Use caution with patients who receive CYP3A4 substrates with a narrow therapeutic index.

Crizotinib is an inhibitor of CYP2B6 in vitro. Use caution with co-administered drugs that are predominantly metabolized by CYP2B6.

Studies demonstrate that crizotinib is a substrate of P-gp and a weak BCRP inhibitor, however the potential to cause drug-drug interactions at therapeutic doses is low. Crizotinib inhibited P-gp, OCT1, and OCT2 in vitro at clinically relevant concentrations. Use caution with co-administration of P-gp, OCT1, and OCT2 substrates.

5.1.9 Side Effects

See Section **Error! Reference source not found.** for side effects.

6. Translational Studies

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

7. References

1. Birchmeier, C., Birchmeier, W., Gherardi, E., and Vande Woude, G.F. (2003). Met, metastasis, motility and more. Nature reviews Molecular cell biology *4*, 915-925.
2. Camidge D.R., Ou S.I., Shapiro G, Otterson G.A., et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). J Clin Oncol 32:5s, 2014 (suppl; abstr 8001)
3. Cappuzzo, F., Janne, P.A., Skokan, M., Finocchiaro, G., Rossi, E., Ligorio, C., Zucali, P.A., Terracciano, L., Toschi, L., Roncalli, M.*, et al.* (2009). MET increased gene copy number and primary resistance to gefitinib therapy in non-small-cell lung cancer patients. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO *20*, 298-304.
4. Catenacci, D.V., Henderson, L., Xiao, S.Y., Patel, P., Yauch, R.L., Hegde, P., Zha, J., Pandita, A., Peterson, A., and Salgia, R. (2011). Durable complete response of metastatic gastric cancer with anti-Met therapy followed by resistance at recurrence. Cancer discovery *1*, 573-579.
5. Catenacci, D.V., Liao, W.L., Thyparambil, S., Henderson, L., Xu, P., Zhao, L., Rambo, B., Hart, J., Xiao, S.Y., Bengali, K.*, et al.* (2014). Absolute quantitation of Met using mass spectrometry for clinical application: assay precision, stability, and correlation with MET gene amplification in FFPE tumor tissue. PloS one *9*, e100586.
6. Chi AS, Batchelor TT, Kwak EL, et al. Rapid radiographic and clinical improvement after treatment of a MET-amplified recurrent glioblastoma with a mesenchymal-epithelial transition inhibitor. J Clin Oncol 2011;30:e30-3.

7. Comoglio, P.M., Giordano, S., and Trusolino, L. (2008). Drug development of MET inhibitors: targeting oncogene addiction and expedience. Nature reviews Drug discovery *7*, 504-516.
8. Cui JJ, Tran-Dube M, Shen H, et al. Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). J Med Chem 2011;54:6342-63.
9. Engelman, J.A., Zejnullahu, K., Mitsudomi, T., Song, Y., Hyland, C., Park, J.O., Lindeman, N., Gale, C.M., Zhao, X., Christensen, J.*, et al.* (2007). MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science *316*, 1039-1043.
10. Gandhi L, Janne PA. Crizotinib for ALK-Rearranged Non-Small Cell Lung Cancer: A New Targeted Therapy for a New Target. Clin Cancer Res 2012.
11. Graziano, F., Galluccio, N., Lorenzini, P., Ruzzo, A., Canestrari, E., D'Emidio, S., Catalano, V., Sisti, V., Ligorio, C., Andreoni, F.*, et al.* (2011). Genetic activation of the MET pathway and prognosis of patients with high-risk, radically resected gastric cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology *29*, 4789-4795.
12. Johnson JL, Pillai S, Chellappan SP (2012). Genetic and Biochemical Alterations in Non-Small Cell Lung Cancer. Biochemistry Research International. 2012;2012:940405. doi:10.1155/2012/940405.
13. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-703.
14. Lennerz, J.K., Kwak, E.L., Ackerman, A., Michael, M., Fox, S.B., Bergethon, K., Lauwers, G.Y., Christensen, J.G., Wilner, K.D., Haber, D.A.*, et al.* (2011). MET amplification identifies a small and aggressive subgroup of esophagogastric adenocarcinoma with evidence of responsiveness to crizotinib. Journal of clinical oncology : official journal of the American Society of Clinical Oncology *29*, 4803-4810.
15. Naran, S., Zhang, X., and Hughes, S.J. (2009). Inhibition of HGF/MET as therapy for malignancy. Expert opinion on therapeutic targets *13*, 569-581.
16. Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-6.
17. Sampson ER, Martin BA, Morris AE, et al. The orally bioavailable met inhibitor PF-2341066 inhibits osteosarcoma growth and osteolysis/matrix production in a xenograft model. J Bone Miner Res 2011;26:1283-94.
18. Scagliotti G, von Pawel J, Novello S, Ramlau R, Favaretto A, Barlesi F, Akerley W, Orlov S, Santoro A, Spigel D, Hirsh V, Shepherd FA, Sequist LV, Sandler A, Ross JS, Wang Q, von Roemeling R, Shuster D, Schwartz B. Phase III Multinational, Randomized, Double-Blind, Placebo-Controlled Study of Tivantinib (ARQ 197) Plus Erlotinib Versus Erlotinib Alone in Previously Treated Patients With Locally Advanced or Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2015 Aug 20;33(24):2667-74.
19. Sen B, Peng S, Saigal B, Williams MD, Johnson FM. Distinct interactions between c-Src and c-Met in mediating resistance to c-Src inhibition in head and neck cancer. Clin Cancer Res 2011;17:514-24.

20. Shaw ATC, D.R.; Engelman, G.A. Clinical activity of crizotinib in advanced non-small cell lung cancer (NSCLC) harboring ROS1 gene rearrangement. In: 2012 ASCO Annual Meeting. Chicago, IL: Journal of Clinical Oncology 2012:Abstr 7508.
21. Smolen, G.A., Sordella, R., Muir, B., Mohapatra, G., Barmettler, A., Archibald, H., Kim, W.J., Okimoto, R.A., Bell, D.W., Sgroi, D.C.*, et al.* (2006). Amplification of MET may identify a subset of cancers with extreme sensitivity to the selective tyrosine kinase inhibitor PHA-665752. Proceedings of the National Academy of Sciences of the United States of America *103*, 2316-2321.
22. Spigel DR, Edelman MJ, O'Byrne K et al;.Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial. J Clin Oncol 32:5s, 2014 (suppl; abstr 8000).
23. Tanizaki J, Okamoto I, Okamoto K, et al. MET tyrosine kinase inhibitor crizotinib (PF-02341066) shows differential antitumor effects in non-small cell lung cancer according to MET alterations. J Thorac Oncol 2011;6:1624-31.
24. Zou HY, Li Q, Lee JH, et al. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. Cancer Res 2007;67:4408-17.

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Appendix I

Patient Pill Calendar

Storage: Store at Room Temperature

Pill Calendar Directions

1. Take your scheduled dose of each capsule. If you take your capsules twice a day, the capsules must be taken 12 hours apart.
2. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses.
3. Please bring the empty bottle or any leftover capsules and your pill calendar to your next clinic visit.
4. Swallow capsules whole and do not take if the capsules are broken.
5. Take with or without food. Taking with food may decrease nausea.
6. If you vomit after a study dose, another dose should not be taken; instead, wait and resume drug dosing at your next scheduled dose.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsules. **Note the times and the number of capsules 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 capsules and your completed pill calendar to your doctor's visits.

Crizotinib

DAY	Date			Time capsules taken		Number of capsules 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								
11								
12								
13								
14								
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28								

Patient Signature: _____ Date: _____

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Appendix II

CYP3A4 Inducers and Inhibitors

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 agent on these lists.

List of CYP3A4 Inducing Agents:

Carbamazepine
Dexamethasone
Ethosuximide
Glucocorticoids
Griseofulvin
Modafinil
Naficillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbitol
Phenylbutazone
Phenytoin
Primidone
Progesterone
Rifabutin
Rifampin
Rifapentine
Rofecoxib
St. John's Wort
Sulfadimidine
Sulfinpyrazone
Tipranavir
Troglitazone

List of CYP3A4 Inhibitors:

Amiodarone
Cimetidine
Ciprofloxacin
Clarithromycin
Delavirdine
Diethyl-dithiocarbamate
Diltiazem
Erythromycin
Fluconazole
Fluvoxamine
Gestodene
Grapefruit or Grapefruit juice
Indanvir
Itraconazole
Ketoconazole
Mibefradil
Mifepristone
Nefazodone
Nelfinavir
Norfloxacin
Norfluoxetine
Ritonavir
Roxithromycin
Saquinavir
Troleandomycin
Voriconazole
Warfarin
Amprenavir
Atazanavir
Miconazole
Telithromycin
Verapamil

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Rev. Add13
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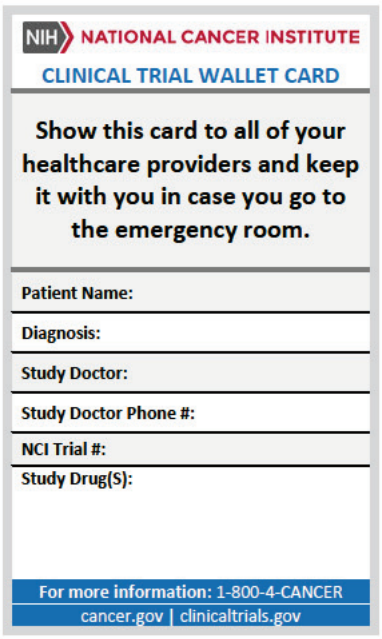
Appendix III

PATIENT CLINICAL TRIAL WALLET CARD


NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

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Appendix IV

Medications That May Cause QTc Prolongation

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral®
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®
Methadone /Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone /Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol /Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Procainamide /Procan®	Ofloxacin /Floxin®	
Quinidine /Cardioquin®	Ondansetron /Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol /Betapace®	Paliperidone /Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity®	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine /Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

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Appendix V

Actionable Mutations for Sub-Protocol EAY131-C1

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
MET	MET	CNV	2	