January 25, 2019

Martha Kruhm, MS RAC

Head, Protocol and Information Office

Quality Assurance Section

CTEP, DCT, NCI

6130 Executive Blvd, EPN Room 7000

Bethesda, MD 20892

Dear Dr. John J. Wright:

Enclosed is Addendum #18 to EAY131-G, *Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol F: Phase II Study of Crizotinib in Patients with ROS1 Translocations (Other Than Patients with Non-Small Cell Lung Cancer).*

This addendum is in response to Dr. John J. Wright's January 22, 2019 Request for Rapid Amendment for Crizotinib.

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

	Section	**Change**
1.	Cover Page	Updated Version Date.
2.	3.3	Updated the Crizotinib CAEPR list with Version 2.3, October 30, 2018.

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

	Section	**Change**
1.	Page 1	Updated Version Date.
2.	What possible risks can I expect from taking part in this study?	Updated the Crizotinib risk list with Version Date October 30, 2018.

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-G so ECOG-ACRIN may activate it promptly.

Thank you.

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Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Enclosure

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

EAY131-G

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol G: Phase II Study of Crizotinib in Patients with ROS1 Translocations (Other Than Patients with Non-Small Cell Lung Cancer)

TREATMENT SUBPROTOCOL CHAIR: Aaron Mansfield, MD
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TRANSLATIONAL CHAIR: Patrick Forde, MD, MBBCh

Version Date: January 25, 2019
NCI Update Date: August 12, 2015

Rev. 8/15 **NOTE: This subprotocol (EAY131-G) should be used in conjunction with the MATCH Master Protocol (EAY131).**

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

SUBPROTOCOL ACTIVATION DATE

August 12, 2015

SUBPROTOCOL PRE-ACTIVATION DATE

May 29, 2015
Update #1 – Incorporated Prior to Activation
Addendum #1 – 8/15
Update #2 – 8/15
Addendum #2 – 2/16
Addendum #3 – 5/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #11 – 8/17
Addendum #13
Addendum #18

Agent	IND#	NSC#	Supply
Crizotinib		749005	NCI Supplied

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Schema

Cycle = 28 days
Accrual Goal: 35

1. Introduction

1.1 Crizotinib

Crizotinib is an ATP-competitive small-molecule oral inhibitor of the anaplastic lymphoma kinase, c-MET/hepatocyte growth factor receptor (HGFR), Recepteur d'Origine Nantais (RON), and ROS receptor tyrosine kinases and their oncogenic variants (e.g., c-MET/HGFR mutations and ALK or ROS1 fusion proteins). The rationale for use of this mechanism to treat cancer is supported by an emerging paradigm in oncology that robust clinical efficacy can be obtained with well-tolerated inhibitors directed toward oncogenic tyrosine kinases that are genetically altered through activating mutations, gene translocations, or gene amplification.

Clinical Experience with Crizotinib

Crizotinib has been tested in numerous phase I, II and III studies in patients with advanced solid tumors. More than 1511 advanced NSCLC patients have received crizotinib on clinical trials at the dosage of 250mg BID that is approved for advanced ALK-rearranged NSCLC. In the first report of crizotinib for ALK-rearranged NSCLC there was an overall response rate of 57% and a 6-month progression free survival of 72% amongst 82 treated patients.[1] An update of this phase 1 trial which included a total of 149 patients reported an overall response rate of 60.8% and a median duration of response of 49.1 weeks.[2] In a separate trial that compared crizotinib in 173 patients to chemotherapy in 174 patients, all with metastatic ALK-rearranged NSCLC, there was a response rate of 65% in the criztonib group compared to 20% in the chemotherapy group. Additionally, median progression free survival was 7.7 months in the crizotinib group compared to 3.0 months in the chemotherapy group.[3] There are few data available on the effects of crizotinib for patients with ROS1-rearranged metastatic NSCLC. The largest study that has been published included 50 patients and demonstrated a 72% response rate and median progression free survival of 19.2 months.[4] ROS1 rearrangements have been identified in other malignancies. There were three patients out of 33 with inflammatory myofibroblastic tumors that harbored a ROS1 rearrangement. The one patient in this study for whom treatment data were available obtained an objective response with crizotinib.[5]

Pharmacokinetics & Metabolism

After a single crizotinib dose of 250 mg, Cmax (peak plasma concentration) was achieved at a median of 4 h, and was associated with a geometric mean terminal half life at steady state of 42 hours.[1-2, 6-7] Age, gender, race, or body weight do not appear to affect crizotinib pharmacokinetics. At the licensed dose of 250 mg BID PO, crizotinib reaches steady state within 15 days. Crizotinib exhibits non-linear PK with reductions noted in CL/F with multiple dosing compared with single dosing. This may be due to auto-inhibition of CYP3A. Crizotinib PK in ALK-positive NSCLC patients was similar to that seen in patients with other tumor types. The concentration-time profiles and PK parameters of crizotinib in Chinese patients were similar to those observed in Asian (mainly Korean and Japanese) and non-Asian patients.

After oral dosing, crizotinib is absorbed with peak plasma concentration occurring between 4-6 hours under fasted condition. The presence of food did not result in clinically meaningful changes in crizotinib PK therefore crizotinib may be taken with or without food.

Crizotinib is highly bound to plasma proteins and is predominantly metabolized by CYP3A. Approximately 53.5% of orally administered crizotinib is excreted unchanged in feces.

Safety, Adverse Events and Efficacy of Crizotinib

Crizotinib has primarily been utilized in the setting of patients with ALK rearrangements. In the expanded cohort phase I trial, most subjects tolerated crizotinib well with grade 1 nausea (52%) and diarrhea (46%) being the most common side effects.[1,2] Additionally, 41% of subjects experienced grade 1 visual disturbances most commonly described as trails of light following moving objects. There was one grade 4 elevation in alanine aminotransferase, and one grade 3 episode of pneumonitis. In this trial there was an overall response rate of 57% and a 6-month progression free survival of 72%. Follow up data from this study were reported in 2012 and adverse events are detailed in Table 1. In a phase III study comparing crizotinib to chemotherapy for patients with NSCLC and ALK rearrangements, 172 patients tolerated criztonib relatively well.[3] The most common grade 3 or 4 event was elevated aminotransferase levels (16%). Less common grade 3 or 4 events included nausea (1%), vomiting (1%), constipation (2%), fatigue (2%), dizziness (1%) and dyspnea (4%). The most common adverse events (all grades) were visual disturbances (60%) and diarrhea (60%). In this trial, the patients who received crizotinib had a 65% response rate and a median progression free survival of 7.7 months. Similarly, in a phase I clinical trial for 50 patients with NSCLC and ROS1 rearrangements, crizotinib was well tolerated.[4] There was a similar side effect profile. No grade 4 or 5 events were observed. Grade 3 vomiting or elevated aspartate aminotransferase was seen in one patient each, elevated alanine aminotransferase in two patients, and hypophosphatemia or neutropenia in five patients each. The most common side effect again was grade 1 visual disturbances (82%). There was a 72% response rate and median progression free survival of 19.2 months observed in this clinical trial. Less common adverse events have been described with crizotinib use including hypogonadism and decreased testosterone levels in males.[8]

Adverse Events			
Study & Population	Selected Adverse Events	All Grades	Grade 3 & 4
Kwak et al. NEJM 2010, Camidge et.al Lancet Oncol 2012[1, 2] Phase I ALK-rearranged NSCLC N=149	Any Adverse Event	97%	24%
	Visual Effects	64%	0%
	Nausea	56%	< 1%
	Diarrhea	50%	0%
	Vomiting	39%	< 1%
	Peripheral edema	30%	0%
	Constipation	28%	< 1%
	Reduced appetite	16%	0%
	Fatigue	16%	1%
	Increased ALT	12%	4%
	Increased AST	10%	3%
	Pnemonitis	< 1%	< 1%
Shaw et al. NEJM 2013[5] Phase III 2nd line ALK-rearranged NSCLC N=172	Visual Effects	60%	0%
	Diarrhea	60%	0%
	Nausea	55%	1%
	Constipation	42%	2%
	Elevated ALT/AST	38%	16%

1.2 Supporting Preliminary Data

Preclinical Data

Crizotinib has been studied in a variety of in vitro and in vivo model systems to determine potency for inhibition of ALK, c-MET/HGFR, RON, or ROS1 RTK activity, kinase selectivity, antitumor efficacy, PK/PD relationships, and mechanism of action. Crizotinib demonstrated potent concentration-dependent inhibition of the kinase activity of ALK, c-MET/HGFR, RON, and ROS1 in biochemical assays and inhibited phosphorylation and kinase dependent function in cell-based assays. Crizotinib demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cells lines exhibiting ALK fusion variants (EML4-ALK) or NPM-ALK), ROS1 fusion variants, or exhibiting amplification of the ALK or c-MET/HGFR gene locus. In vivo, crizotinib demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting ALK fusion variants (EML4-ALK or NPM-ALK), ROS1 fusion variants, or exhibiting amplification of the ALK or c-MET/HGFR gene locus. In vivo, crizotinib demonstrated antitumor efficacy, including marked cytoreductive antitumor activity, in mice bearing tumor xenografts that expressed ALK fusion variants or activated c-MET/HGFR. The anti-tumor efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion variants (EML4-ALK or NPM-ALK) or c-MET/HGFR in tumors in vivo. The collective rationale for investigation of crizotinib in clinical studies is built on genetic alteration of its molecular targets, its predicted ability to target multiple processes that are common to cancer progression, and preclinical efficacy data.

Rationale for Crizotinib in ROS1-translocated Tumors

Several lines of evidence suggest that ROS1 may represent another therapeutic target of crizotinib. ROS1 encodes a transmembrane protein with an extracellular domain that is partially analogous to fibronectin.[8] Although the function of wild type ROS1 is poorly understood, it is speculated that ROS1 might translate adhesion events to intracellular signaling because of the structural similarities to cell adhesion molecules. The kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites, and due to this homology, crizotinib binds with high-affinity to both ALK and ROS1.[8] In cell-based assays for inhibition of autophosphorylation of different kinase targets, both ALK and ROS1 are sensitive to crizotinib, with a half-maximal inhibitory concentration of 40 to 60nM.[8] Preclinical studies have shown that crizotinib potently inhibits ROS1 signaling and cell viability in cell lines expressing ROS1 fusions.[9-12]

The ROS1 proto-oncogene has been identified to be translocated in non-small cell lung cancers and is predicted to exhibit the properties of an “oncogenic driver”. In published studies, the frequency of ROS1-positive NSCLC has been examined in 2 studies ranging from 1.7% (18/107) to 2.6% (17/656).[10,13] Patients with adenocarcinoma of lung have demonstrated remarkable responses to crizotinib when their tumor has a ROS1 translocation. An expansion cohort of 50 response-evaluable advanced ROS1-positive NSCLC patients with crizotinib 250 mg BID (NCT00585195) was recently reported, including an ORR of 72% (95% CI: 58–84), with 3 complete responses and 33 partial responses.[6] The median duration of response was 17.6 months (95% CI, 14.5 to not reached), with 25 patients (50%) still in follow-up for progression. Among 30 tumors that were tested, 7 ROS1 fusion partners: 5 known and 2 novel partner genes were identified.[6] The most common ROS1 fusion partner was the gene encoding CD74. Other partner genes included SDC4, EZR, SLC34A2, TPM3, LIMA1, and MSN.

It is anticipated that the frequency of ROS1 translocations across all tumors is relatively rare. However, there have been reports of ROS rearrangements in cancers such as CMML (70%), gastric cancer (5), glioblastoma (incidence unknown), NSCLC (1-2%), cholangiocarcinoma (9%), ovarian cancer (0.5%), colorectal cancer (1%), inflammatory myofibroblastic tumor, angiosarcoma and epithelial hemangioendothelioma.[14-17] Additional ROS1 fusion partner genes identified in these malignancies included CCDC6, CEP85L, FIG (aka GOPC), KDELR2, KIF5B, LRIG3, TFG, and YWHAE. The dramatic responses and duration of benefit for patients with ROS1 translocations in non-small cell lung cancer argue that, though infrequent, ROS translocations may be a substantial “driver” mutation, and thus, across cancers, and with crizotinib treatment, there may be a response/longer progression-free survival time in any tumor harboring a ROS translocation.

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: 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.

Rev. 8/15

2.1 Eligibility Criteria

Rev. Add13

_____ 2.1.1 Patients must be positive for translocation or inversion events involving the ROS1 gene via the MATCH Master Protocol and described in Appendix IV. See Appendix IV for information on the ROS1 translocations and inversions and corresponding LOEs.

Rev. 2/16

_____ 2.1.2 Patients must not have NSCLC with ROS1 rearrangements.

Rev. 8/15

_____ 2.1.3 Patients with a history of interstitial lung disease or pneumonitis are excluded.

Rev. 2/16

_____ 2.1.4 Patient must fulfill all eligibility criteria outlined in Section 3.1 of the MATCH Master Protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

Rev. 8/15

_____ 2.1.5 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).

Date of ECG: _____

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

_____ 2.1.7 Patients using drugs or foods that are known potent CYP3A4 inhibitors or inducers will be excluded (See Appendix II)

_____ 2.1.8 Patients must not have had prior therapy with any ROS1 inhibitor including crizotinib, ceritinib, foretinib, cabozantinib, AP26113, ASP3026, WZ-5-126, TAE684, KIST301072, KIST301080, AZD1480, PF-06463922, RXDX-101 and PF-3922

_____ _____

Physician Signature Date

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

3. Criztonib 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, ie, no break in dosing. 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.

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. 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.

3.2 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 G

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 G 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 Crizotinib, or within 28 days of the subject'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 Master protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131 – Subprotocol G specific expedited reporting exceptions:

For subprotocol G, 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. 5/16
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	

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%)**	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema face			***Edema face (Gr 2)***
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		

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%)**	
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	
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*.
ALT elevation with total bilirubin < 2 X ULN (in the absence of cholestasis or hemolysis) §	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 dose until toxicity is grade 1, or has returned to baseline, then resume treatment by reducing the dose by one dose level. If Grade 3 ALT elevation recurs reduce further (at most by 2 dose levels from initial dose level). If recurrence at dose level -2, discontinue permanently. If Grade 3 ALT elevation does not recur after at least 4 weeks, the dose may be escalated by single dose level increments up to the initial dose level.	See Grade 3.
ALT elevation concurrent with total bilirubin elevation ≥ 2 X ULN (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	Interrupt crizotinib until recovery to baseline. Assess and correct electrolytes and concomitant medications. Resume treatment by reducing the dose by one dose level, unless an alternative cause for QTc prolongation is found and corrected, resume at the same dose level.	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+.
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.

3.5 Supportive Care

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

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 Section 3.4 for instructions on dose modifications.

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3.5.3 Bradycardia:

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 (same pathogens as 3.6.4.1)
- 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.

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

NOTE: In addition to the study parameters listed in the MATCH Master Protocol at Step 0, the below parameters must also be performed for patients on 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).

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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).

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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.

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D. Disease measurements are repeated every 2 cycles for first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information

on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

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

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

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- 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 subprotocol prior to submitting the clinical drug request to PMB.

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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 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 Crizotinib (NSC #749005)

5.1.1 Other Names

Xalkori®, PF-02341066

5.1.2 Classification

ALK inhibitor

5.1.3 Mode of Action

Crizotinib is a selective ATP-competitive small –molecule inhibitor of anaplastic lymphoma kinase (ALK), c-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 c-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.

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 Incompatibilities

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

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See Section 3.3 for side effects.

6. Translational Studies

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

7. References

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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol G: Criztonib

Appendix I

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Pill Calendar

Storage: Store at Room Temperature

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Pill Calendar Directions

1. Take your scheduled dose of each capsule.
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 (do not crush, dissolve, or open capsules).
5. Take with or without food. Taking with food may decrease nausea.

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 capsule. **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								
15								
16								
17								
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19								
20								
21								
22								
23								
24								
25								
26								
27								
28								

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol G: Criztonib

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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Appendix III

Information On Possible Drug Interactions

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

The patient _____ is enrolled on a clinical trial using the experimental agents **Crizotinib.** *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.*

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

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

Crizotinib interacts with certain specific enzymes in your liver.

- The enzymes in question are ***CYP 2B6 and 3A4 enzymes.*** Crizotinib blood levels are affected (could be lower or higher) by some of these enzymes and taking crizotinib with some medicines can raise or lower the levels of crizotinib or other medicines you take (drug-drug interaction). Crizotinib must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzymes.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
        - Crizotinib should not be taken with any other drugs that are strong inducers or inhibitors of CYP 3A4. Prohibited medications include azole antifungals, some antiepileptic drugs, some antibiotics and some immunosuppressants as well as over the counter drugs such as St. John's Wort. Please check with the study investigator before prescribing or dispensing strong inhibitors/inducers of CYP 3A4. Grapefruit or grapefruit juice should also be avoided.
    - Crizotinib is considered an inhibitor of CYP 2B6 and 3A4, meaning that it can increase the levels of drugs that are substrates of CYP 2B6 or 3A4 with a narrow therapeurtic index. This can lead to harmful side effects of those medications. Avoid using or prescribing drugs that could be affected including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus.

- Crizotinib inhibits the transport proteins P-glycoprotein, OCT1 or OCT2. Medications that are substrates for these transport proteins must be used with caution.

- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any prohibited medicines that are considered "strong inducers/inhibitors or substrates of ***CYP 2B6 or 3A4***."
- Your prescribers should look at a frequently-updated drug reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
  - If you take acetaminophen regularly: You should not take more than 3 grams (six 500 mg pills, or nine 325 mg pills) a day if you are an adult or 2.4 grams (four 500 mg pills, or seven 325 mg pills) a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
  - If you take herbal medicine regularly: You should not take St. John's wort while you are taking crizotinib.
  - Avoid consumption of grapefruit, grapefruit juice, and Seville oranges.
  - Avoid antacids and tell your doctor if you are taking any medicine for heartburn symptoms.

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

  Crizotinib 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.

  Your study doctor's name is

  _____

  and he or she can be contacted at

  _____

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent **crizotinib.** This clinical trial is sponsored by the NCI. Crizotinib interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Crizotinib interacts with specific liver enzymes called **CYP 2B6 and 3A4,** and must be used very carefully with other medicines that interact with these enzymes.
- Before you start the study, your study doctor will work with your regular prescriber to switch any prohibited medicines that are considered "strong inducers/inhibitors or major substrates of **CYP 2B6 or 3A4** with a narrow therapeutic index" or will use caution when combining Crizotinib with medications that are substrates of the transporters P-glycoprotein, OCT1 or OCT2.
- Avoid consumption of grapefruit, grapefruit juice or Seville oranges while taking crizotinib.
- Before prescribing new medicines, your regular prescribers should check a frequently-updated drug resource for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is

  _____

  and can be contacted at

  _____

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Actionable Mutations for Sub-Protocol EAY131-G

Other novel ROS1 fusions not listed in the below table but identified by one of the designated outside laboratories as described in the MATCH Master Protocol will also be considered actionable mutations (aMOIs) at Level of Evidence Code 3. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Gene	Variant ID	Variant Description	Level of Evidence
ROS1	TMEM106B-ROS1.T3R35	Fusion	1
ROS1	SDC4-ROS1.S4R34.COSF1280	Fusion	1
ROS1	SDC4-ROS1.S2R32.COSF1265	Fusion	1
ROS1	YWHAE-ROS1.Y4R36	Fusion	1
ROS1	MSN-ROS1.M9R34	Fusion	1
ROS1	CEP85L-ROS1.C8R36	Fusion	1
ROS1	CCDC6-ROS1.C5R35.1	Fusion	1
ROS1	KDELR2-ROS1.K5Rintron34	Fusion	1
ROS1	KDELR2-ROS1.K5R35	Fusion	1
ROS1	PWWP2A-ROS1.P1R36	Fusion	1
ROS1	SDC4-ROS1.S2R34	Fusion	1
ROS1	HLA_A-ROS1.H7R34	Fusion	1
ROS1	SLC34A2-ROS1.S4R34.COSF1198	Fusion	1
ROS1	GOPC-ROS1.G8R35.COSF1139	Fusion	1
ROS1	EZR-ROS1.E10R35	Fusion	1
ROS1	SDC4-ROS1.S4R32.COSF1278	Fusion	1
ROS1	KIAA1598-ROS1.K11R36	Fusion	1
ROS1	CLIP1-ROS1.C19R36	Fusion	1
ROS1	CD74-ROS1.C6R34.COSF1200	Fusion	1
ROS1	PPFIBP1-ROS1.P9R35	Fusion	1
ROS1	LRIG3-ROS1.L16R35.COSF1269	Fusion	1
ROS1	TPM3-ROS1.T3R36	Fusion	1
ROS1	NFKB2-ROS1.N13R36	Fusion	1
ROS1	SLC34A2-ROS1.S13R34.COSF1261	Fusion	1
ROS1	CD74-ROS1.C6R35.COSF1478	Fusion	1

Gene	Variant ID	Variant Description	Level of Evidence
ROS1	SLC34A2-ROS1.S13R36	Fusion	1
ROS1	ZCCHC8-ROS1.Z2R36	Fusion	1
ROS1	CD74-ROS1.C6R32.COSF1202	Fusion	1
ROS1	CD74-ROS1.C4R33.NGS	Fusion	1
ROS1	ERC1-ROS1.E11R36	Fusion	1
ROS1	SLC34A2-ROS1.S13R32.COSF1259	Fusion	1
ROS1	TPM3-ROS1.T7R35.COSF1273	Fusion	1
ROS1	TFG-ROS1.T4R35	Fusion	1
ROS1	EZR-ROS1.E10R34.COSF1267	Fusion	1
ROS1	SLC34A2-ROS1.S4R32.COSF1196	Fusion	1
ROS1	NCOR2-ROS1.N7R36	Fusion	1
ROS1	MYO5A-ROS1.M23R35	Fusion	1
ROS1	GOPC-ROS1.G4R36.COSF1188	Fusion	1

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Appendix V

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®	

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 /Pronestyl®	Octreotide /Sandostatin®	
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®	