COLUMBIA UNIVERSITY MEDICAL CENTER

Herbert Irving Comprehensive Cancer Center Protocol

Phase II Trial of Adjuvant Crizotinib in High-Risk Uveal Melanoma Following Definitive Therapy

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Columbia University Medical Center
Herbert Irving Comprehensive Cancer Center

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TITLE: Phase II Trial of Adjuvant Crizotinib in High-Risk Uveal Melanoma Following Definitive Therapy

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Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

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Signature of Principal Investigator Date

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Principal Investigator Name (Print)

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Table of Contents

1. PROTOCOL SUMMARY AND/OR SCHEMA

The primary purpose of this single-arm study is to assess the relapse-free survival (RFS) of adjuvant crizotinib in patients with uveal melanoma who are at high-risk of recurrence following definitive therapy with surgery or radiotherapy. Patients with class 2 tumors as defined by gene expression profiling (GEP; DecisionDx-UM, Castle Biosciences Inc, Friendswood, TX) who have undergone definitive therapy, who do not have evidence of metastatic disease, and who have adequate renal, hepatic, and hematologic function will be eligible for study participation.

The study will be conducted in 3 phases:

1. **Active Therapy:** During the active therapy phase of the study, patients will receive 48 weeks (12 four-week cycles) of crizotinib 250 mg PO BID. Patients will be evaluated by routine blood work and physical examination every 4 weeks while they are receiving crizotinib. Imaging studies, optimally including a chest CT scan (with or without contrast) and an abdominal/pelvic MRI with contrast, will be performed at baseline and every 12 weeks.

2. **Follow-Up:** During the follow-up phase of the study, patients will be seen on an every 3 month basis until distant disease recurrence, withdrawal of consent, or study closure. Imaging studies, optimally including a chest CT scan (with or without contrast) and an abdominal/pelvic MRI with contrast, will be performed every 12 weeks until the time of distant disease recurrence, withdrawal of patient consent, or study closure.

3. **Survival Phase**: Patients who have distant disease recurrence during follow-up will then be contacted every 3 months (+/- 2 weeks) to obtain vital status for at least 36 months from the start of active therapy.

Patients with tumors of 12mm basal diameter or greater and a class 2 signature have a median time to recurrence of 32 months (personal communication, J. William Harbour, MD, Bascom Palmer Eye Institute) and represent an ideal patient population for a clinical trial testing the efficacy of an adjuvant therapy in this disease. We hypothesize that the addition of crizotinib will increase the 32 month RFS by 25%. Thus, a 32 month RFS of 50% would be considered not promising and a 32 month RFS of 75% or greater would be considered promising. A single stage design based on a binomial probability estimate will be utilized with an alpha of 0.05 and a beta 0.11. This design will require 30 patients. At the end of the study, if at least 20 out of 30 patients are relapse-free at or after 32 months, this adjuvant treatment with crizotinib will be considered worthy of further study. For the purposes of this study, distant disease relapse is defined as the development of tumor growth or recurrence at a site distant from the affected eye. Patients who develop recurrent metastatic disease at any site will be considered treatment failures.

2. OBJECTIVES AND SCIENTIFIC AIMS

- **Primary**

- To determine the 32 month rate of distant relapse in patients with uveal melanoma who are at high risk of recurrence following definitive therapy with surgery or radiation who receive adjuvant crizotinib.

- **Secondary**
  - To determine the overall survival and disease specific survival in this patient population.
  - To evaluate safety and toxicity of adjuvant treatment with crizotinib.
    To describe the quality of life in patients receiving crizotinib using the Functional Assessment of Cancer Therapy - Melanoma (FACT-M) questionnaire

- **Correlative**
  - To collect patient serum and plasma for circulating tumor DNA and companion normal gene expression levels
  - To investigate changes in target genes at baseline in primary tumors and at recurrence in metastatic samples after crizotinib therapy
  - To establish cell lines or murine xenografts of metastatic recurrences

3. BACKGROUND AND RATIONALE

3.1 Uveal Melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults, and arises from melanocytes within the choroid plexus of the eye.[1] Melanomas of the ocular and adnexal structures comprise approximately 5% of all melanomas and are biologically and prognostically distinct from cutaneous melanoma.[2] In the United States, an estimated 2000 patients are diagnosed with this disease each year. Approximately 85% of ocular melanomas are uveal (iris, ciliary body, and choroid) in origin, with primary conjunctival and orbital melanomas being less common.[2,3] Cases are nearly equally distributed between male and female subjects, with a median age at diagnosis of 62 years.[4] The majority (97.8%) of cases of uveal melanoma occurs in the white population, with a white:black incidence ratio of 196:1.

The development of metastasis in this disease is common and occurs in approximately 50% of patients with posterior uveal melanoma within 15 years after the initial diagnosis and treatment.[5] Uveal melanoma is thought to be particularly resistant to systemic treatment, and no systemic therapy has yet been demonstrated to improve survival.[6] Drugs commonly used to treat advanced cutaneous melanoma rarely achieve durable responses in patients with uveal melanoma. Nathan et al compared the outcome between 139 patients with non-uveal melanoma and 16 patients with uveal melanoma who were treated with DTIC, BCNU, cisplatin, and tamoxifen (Dartmouth regimen).[7] The response rates were 33% and 6% respectively. In a review of the MD Anderson Cancer Center experience of 143 treated patients with metastatic ocular melanoma, there was only a single objective response observed.[8] Retrospective reviews of the ECOG and SWOG experiences revealed similar

findings.[9] Because of the lack of effective systemic treatment options, outcomes are poor once metastatic disease occurs, and the median survival from the time of the development of distant metastatic disease is 6 to 12 months.[10-12]

Although it is clear that novel effective therapies are desperately needed for this disease, the development of such therapies has been hampered by the rarity of uveal melanoma. Indeed, over the past decade, only 8 phase II trials in uveal melanoma have been published, with the largest of these trials accruing only 48 patients and none demonstrating significant efficacy in terms of response rate, overall survival or progression-free survival (see table 1 below).

Table 1. Published phase II trials in uveal melanoma.

Investigator	Study Treatment	n	Response Rate	Overall Survival	Progression-Free Survival
Homsi et al, 2010[13]	Docosahexaenoic acid-Paclitaxel	22	4%	9.8 mos	NR
Penel et al, 2008[14]	Imatinib	10	0%	10.8 mos	NR
Schmittel et al, 2006[15]	Gemcitabine/Treosulfan vs Treosulfan	48	2%	NR	2-3 mos
O'Neill et al, 2006[16]	DTIC/Treosulfan	15	0%	NR	3 mos
Schmittel et al, 2005[17]	Gemcitabine/Cisplatin/ Treosulfan	17	0%	NR	3 mos
Schmidt-Hieber et al, 2004[18]	Bendamustine	14	0%	NR	NR
Bedikian et al, 2004[19]	Temozolomide	14	0%	6.7 mos	1.8 mos
Kivelä et al, 2003[20]	Bleomycin/Vincristine/Lomustine/ DTIC + Interferon	22	0%	NR	1.9 mos

Despite our inability to identify effective therapies for this disease thus far, our increasing understanding of the underlying biology of uveal melanoma has led to the identification of a number of novel and promising therapeutic strategies that warrant investigation.

3.2 Prognostic Features Identify Uveal Melanoma Patients at High Risk for Recurrence

Clinical factors that relate to prognosis include location (primary melanomas of the iris connote a better prognosis than those arising from the choroid, and choroidal melanomas fare better than ciliary body melanomas),[21,22] configuration of the tumor (diffuse configuration suggests poor prognosis),[23] and size.[24] Histopathologic features of importance include tumor cell type (spindle morphology connotes a better prognosis than mixed morphology, and mixed morphology fares better than epithelioid morphology),[25,26] extent of mitotic activity,[27] vascular network (absent better than present),[28] tumor-infiltrating lymphocytes (absent better than present),[29] and the presence of extrascleral extension (absent better than present).[22] Nonrandom changes in chromosomes 1, 3, 6, and 8 have been identified by FISH and CGH in uveal melanomas.[30-32] Monosomy 3 and amplification of 8q have been identified as poor prognostic indicators.[31,33] Other prognostic factors include high expression of HLA class I,[34] c-myc,[35] cyclin D1, p53 MDM2,[36] and IGF-IR.[37]

Two independent groups have identified microarray gene expression profiles (GEP) which accurately segregate uveal melanomas into two tumor classes by risk of metastasis.[38,39] Onken et al identified 62 genes that discriminate between tumors that have a low-risk of metastasis (class 1 tumors) and those that are more aggressive and are associated with a higher risk of metastatic death (class 2 tumors).[39] The GEP assay was performed on a sample collected directly from the primary tumor, usually at the time of treatment. In a recent study of 459 cases, the GEP assay was successful in rendering a classification in 446 of 459 cases (97.2%).[40] Among the 13 samples that failed to yield a GEP result, 5 did not adhere to study protocol (improper buffer, handling, or shipping). Of the 446 cases, 276 (61.9%) were class 1 and 170 (38.1%) were class 2. Median follow-up was 17.4 months (mean, 18.0 months). Metastasis was detected in 3 patients (1.1%) with class 1 tumors and 44 patients (25.9%) with class 2 tumors (log rank, $P<0.0001$).

GEP class 2 tumors showed a significant association with other known prognostic factors, including increased patient age, greater tumor diameter and thickness, ciliary body involvement, and mixed/epithelioid cell type. By Kaplan–Meier analysis, GEP class 2 was more strongly associated with metastasis than any of the other prognostic factors that were analyzed, including chromosome 3 status (see **Figure 1** below). By univariate Cox proportional hazards analysis, factors associated with metastasis included advanced patient age ($P = 0.02$), ciliary body involvement ($P = 0.03$), tumor diameter ($P = 0.0003$), tumor thickness ($P = 0.006$), tumor cell type ($P = 0.04$), chromosome 3 status ($P = 0.0002$), and GEP class ($P<10-7$). This analysis was performed on all cases with values reported for a given factor, and there was no significant impact on the results when the analysis was restricted to those cases with complete data for all factors. By multivariate Cox modeling, GEP class ($P = 0.006$) was the only variable that contributed independent prognostic information. Chromosome 3 status did not contribute additional prognostic information that was independent of GEP ($P = 0.2$).

Thus, the use of GEP which is now commercially available, provides a powerful tool to identify those patients at highest risk of disease recurrence. Patients with tumors of 12mm basal diameter or greater and a class 2 signature have a median time to recurrence of 32 months (personal communication, J. William Harbour, MD, Bascom Palmer Eye Institute) and represent an ideal patient population for a clinical trial testing the efficacy of an adjuvant therapy in this disease.

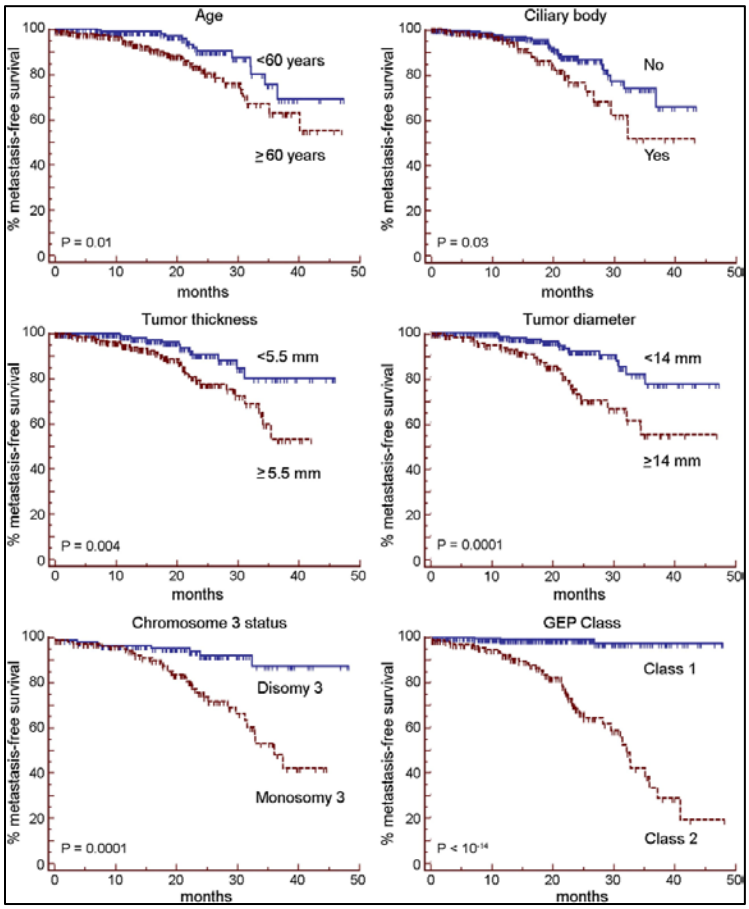

Figure 1. Metastasis free survival is best predicted by GEP Class 1 versus 2.

3.3 The HGF/c-MET Pathway Plays an Essential Role in the Pathophysiology of Uveal Melanoma.

Uveal melanomas overexpress c-MET, or HGF receptor, in 60% - 86% of cases;[41,42] however, activating mutations or genetic amplifications of c-MET do not appear to play a significant role in this disease.[43] The lack of direct gene activation suggests that the MET activation in UM is mostly through an indirect mechanism. c-MET overexpression appears to signify more aggressive disease and activation of the HGF/c-MET pathway in uveal melanoma is associated with greater cell migration capacity and inferior clinical outcomes. Indeed, in a series of 60 patients with resected uveal melanoma, higher levels of c-MET expression were found to be associated with a significantly higher risk of death from metastatic disease.[42]

Hendrix and colleagues first reported in 1998 the expression of c-MET by the more invasive interconverted phenotype of uveal melanoma cell lines, and subsequently showed a mitogenic response to HGF by c-Met expressing cells, but not by those who failed to

express c-Met.[44] Cell migration capacity appears to be enhanced by HGF via activation of phospho-AKT and the downregulation of the cell adhesion molecules e-cadherin and beta-catenin in a dose-dependent fashion.[45] Both c-MET inhibition and AKT inhibition independently inhibited the downregulation of adhesion molecules by HGF and completely abolished the migration of uveal melanoma cell lines, suggesting that activation of p-AKT via the HGF/c-MET axis is involved in HCF-induced uveal melanoma cell migration.[45,46]

Our group evaluated the expression of cMet and its basal phosphorylation status in 6 UM cell lines (**Figure 2A**).[47] All cell lines expressed cMet and pMet, however, expression was greater in cell lines with GNAQ or GNA11 mutations (92.1, Omm1.3, and Omm1). We also investigated the ability of uveal melanoma cells to secrete HGF, the ligand for cMet, by ELISA (**Figure 2B**) and observed that cell lines with GNAQ or GNA11 mutations secreted more HGF than the wild-type cell lines, suggesting that UM cell lines with such mutations may be activating cMet through an autocrine signaling mechanism.

Figure 2. Expression and HGF Secretion of cMet in UM cells. A, cells were grown in serum-free media for 24 hrs and lysed for immunoblot analysis. cMet expression and phosphorylation is generally higher in cell lines with G-protein mutations. B, media from the plates were tested for the presence of HGF by ELISA. All cell lines secreted HGF but average HGF secretion of G-protein mutant cell lines was higher than the wild-type cell lines.

Interestingly, HGF and its receptor tyrosine kinase c-Met play essential roles in the processes of liver embryogenesis and in hepatic regeneration following injury in the adult state, emphasizing their role as both morphogen and mitogen for this organ.[46,48] Because uveal melanoma metastases preferentially involve the liver, the question arises as to whether local factors within the hepatic environment such as HGF or IGF-1 are responsible

for the dominant pattern of metastases seen at this site, and whether inhibition of this pathway could decrease the risk of developing metastatic disease.[49,50]

3.4 Crizotinib

Preclinical Studies. Crizotinib (PF-02341066) is a selective ATP competitive small molecule tyrosine kinase inhibitor of c-MET/hepatocyte growth factor receptor (HGFR) and ALK tyrosine kinases. In pre-clinical studies, crizotinib inhibited cell growth of cell lines with either MET amplification or ALK gene rearrangement.[51] In murine models, there was significant antitumor activity in mice with xenografts expressing activated c-MET or the EML4-ALK gene rearrangement.[51] These promising pre-clinical studies provided rationale for study of this agent in clinical trials.

Phase I and II Clinical Trials. Crizotinib was initially studied as an orally available MET inhibitor in a phase 1 study in various solid tumors, with ALK inhibition seen as an off target effect (MSKCC protocol 07-157). The maximum tolerated dose was established at 250mg orally given twice daily given continuously. The EML4-ALK oncogene was subsequently identified in NSCLC, and upon retrospective molecular typing, two patients with dramatic partial responses were discovered to have the ALK gene rearrangement. An expanded cohort of 82 patients with ALK+ NSCLC was given crizotinib, and had an overall response rate of 56%, with an additional 33% with stable disease.[52] A recent update reported a median progression free survival of 9.2 months on crizotinib.[53] Interim results of a phase II trial of 136 patients with advanced ALK+ NSCLC revealed that 90% of evaluable patients showed target lesion shrinkage.[54] Based on these trials, the FDA recently approved crizotinib for ALK positive metastatic non-small cell lung cancer.

Toxicities. In the phase 1 trial that established the maximum tolerated dose, the dose limiting toxicities included a grade 3 elevation in ALT in one patient and grade 3 fatigue in two patients.[55] The most common adverse events were nausea, emesis, fatigue and diarrhea, which were primarily grade 1-2 in severity. Nausea and emesis were independent of dose or duration of treatment and were effectively managed with supportive medications. Treatment-related vision disturbances, observed in most patients, were grade 1 in severity and were reversible upon discontinuation of crizotinib. The MTD was established at 250mg orally twice daily.

3.5 c-MET Inhibition Impedes Uveal Melanoma Cell Migration.

We tested the effects of downregulation of cMet, ALK and ROS1, targets inhibited by crizotinib, on cell proliferation and migration of UM cell lines.[47] Western blot confirmed decreased cMet in all the cell lines transfected with cMet siRNA (**Figure 3A**), with suppression of ALK and ROS1 observed in cell lines with positive basal expression. While cell viability assays demonstrated no suppression of growth by cMet knockdown (data not shown),22 cMet siRNA significantly inhibited cell migration ($p<0.05$; **Figure 3B**), with statistically non-significant inhibition of migration observed with ALK and ROS1 siRNA.

Next, we utilized doses of crizotinib necessary to selectively inhibit pMet but with no effect on cell growth. After 72 hrs of treatment, all UM cell lines showed a dose-dependent decrease in viability in response to crizotinib at doses >1,000 nmol/L (**Figure 2C**). cMet phosphorylation was inhibited by crizotinib starting at 25 nmol/L, whereas neither ALK nor ROS1 was inhibited at any of the concentrations tested with 24 hours of drug exposure (data not shown). When UM cells were treated with 25 nmol/L of crizotinib in a 24-hr migration assay, a mutation-dependent effect was observed such that only the migration of GNAQ and GNA11 mutant cells lines and not wild-type cell lines (C918 and Mel290), was decreased (**Figure 2D**). However, when treated with 250 nmol/L crizotinib for 24 hrs (conditions under which cell proliferation was still not affected), the migration of all cell lines was inhibited irrespective of mutational status (data not shown), suggesting that GNAQ and GNA11 mutant cells with higher basal activity of cMet are sensitive to lower concentrations of crizotinib.

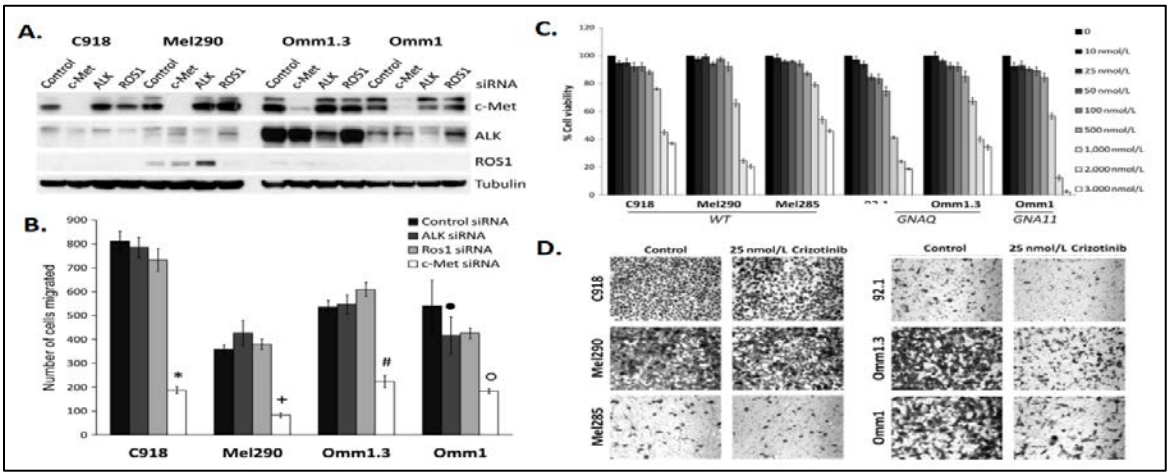

Figure 3. Effects of cMet Inhibition on Cell Migration. A, cells were transfected with control, cMet, ALK, or ROS1 siRNA. Western blot analysis of the lysates verified that all target genes were knocked down by their respective siRNA. B, transfected cells were seeded on Matrigel chambers in triplicates and allowed to migrate for 24 hours into RPMI media containing 10% serum. Migrated cells were then quantitated. Only cMet siRNA knockdown significantly inhibits cell migration. C, UM cells were plated and treated in triplicates with increasing doses of crizotinib for 72 hours in 96-well plates then cell viability was measured as the percentage of untreated controls. Crizotinib inhibited cell proliferation in a dose-dependent manner regardless of genotype only at higher concentrations. The IC50 range is from 750 to 2,000 nmol/L. D, UM cells were seeded on a Matrigel chamber with 0.1% FBS in RPMI and either DMSO or 25 nmol/L crizotinib. Cells were then allowed to migrate for 24 hours into media containing 10% FBS and 50 ng/mL HGF. The migration of GNAQ-mutant UM cells was significantly inhibited with 25 nmol/L crizotinib but not the migration of wild-type cell lines.

3.6 Crizotinib Inhibits the Development and Establishment of Metastases in a Murine Model of Uveal Melanoma

We developed a metastatic model of UM where retro-orbital injection of 10 million OMM1.3 cells labeled with GFP/luciferase results in the development of hepatic metastasis within 6 weeks.[47] Using this model, we treated mice with 50 mg/kg of crizotinib (5 days/week) 1 week after tumor implantation for a total of 8 weeks. Imaging performed at week 11 demonstrated significant suppression of metastatic spread with treatment compared to control mice (**Figures 4A and 4B**) confirmed by necroscopy at week 11 (**Figure 4C**). Importantly, UM tumor growth in the eye of the mice was not inhibited by crizotinib, which mirrors that lack of efficacy in 2 xenograft models of established UM tumors (data not shown).

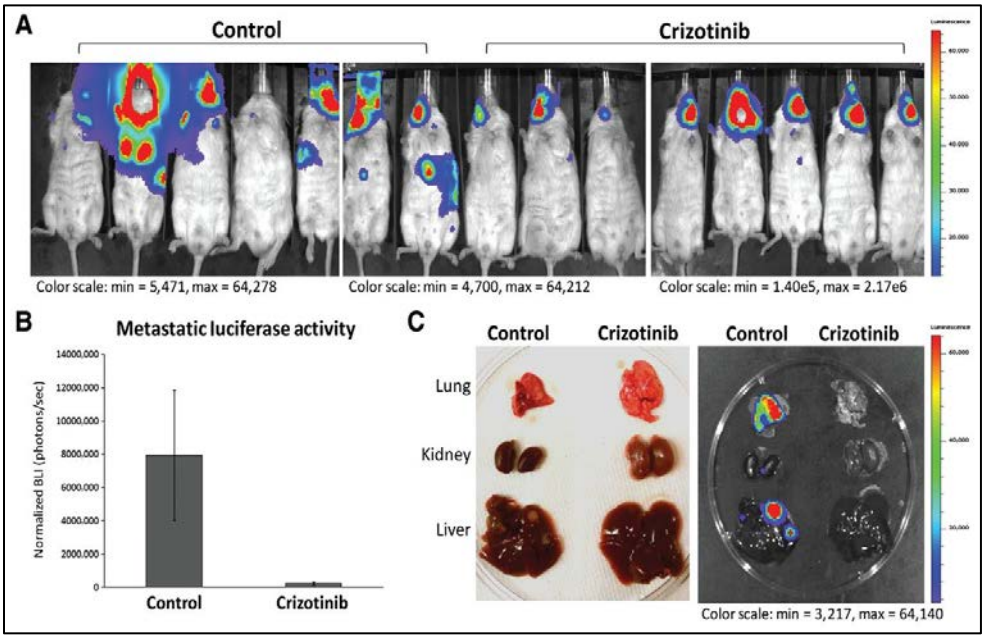

Figure 4. Inhibition of Metastasis by Crizotinib in a Metastatic UM Model. A, bioluminescence imaging at 7 weeks after injection of cells compared progression of metastasis in control- (n=10) and crizotinib-treated (n=12) mice. Control mice have metastasis in the abdominal region, while crizotinib inhibited metastasis. B, bioluminescence intensity was quantified for each mouse and the mean calculated for each cohort. Luciferase activity in metastatic sites was significantly decreased in crizotinib-treated mice compared with the vehicle control (p=0.03). C, necropsy showed macrometastases in the liver and lungs of the controls, whereas none were seen in the crizotinib-treated mice. Bioluminescence imaging of the liver and lungs further illustrates inhibition of metastasis by crizotinib.

We have demonstrated that inhibition of cMET by siRNA and crizotinib results in anti-migratory activity in UM cell lines, and that crizotinib impedes the development of distant metastatic disease to the liver and other sites in a UM mouse model. Given the biological relevance of the HGF/cMET axis in UM combined with the preclinical data supporting the anti-migratory and anti-tumor activity of cMET targeting in this disease, we propose a phase II clinical trial to investigate our hypothesis that cMET inhibition with crizotinib with prevent the establishment and development of metastases in patients with high-risk primary uveal melanoma.

4. OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The primary endpoint of this trial is RFS. Patients with tumors of 12mm basal diameter or greater and a class 2 signature have a median time to recurrence of 32 months (personal communication, J. William Harbour, MD, Bascom Palmer Eye Institute). We hypothesize

that the addition of crizotinib will increase the 32 month RFS by 25%. Thus, a 32 month RFS of 50% would be considered not promising and a 32 month RFS of 75% or greater would be considered promising. A single stage design based on a binomial probability estimate will be utilized, with an alpha of 0.05 and a beta of 0.11. This design will require 30 patients. At the end of the study, if at least 20 out of 30 patients are relapse free at 32 months, this adjuvant treatment crizotinib will be considered worthy of further study.

4.2 **Intervention**

Tumor FNA or enucleation may be performed as standard of care prior to obtaining written informed consent for this trial. GEP will be determined by the DecisionDx-UM gene expression assay as standard of care using the FNA specimen or 5 unstained FFPE slides from the enucleation specimen. Patients with class 2 tumor will be offered participation in this study. Should they be interested in participation, written informed consent will be obtained. Investigational studies including cMET gene expression will be performed subsequently by Castle Biosciences should sufficient material be available.

Patients with class 2 tumors as defined by GEP that are 12mm in basal diameter or greater and who have undergone definitive therapy and who do not have evidence of metastatic disease will receive 12 four-week cycles (total of 48 weeks) of crizotinib 250 mg BID. Patients must have adequate renal, hepatic, and hematologic function for eligibility.

Patients will be evaluated by routine bloodwork and physical examination on a monthly basis while they are receiving crizotinib and will subsequently be seen on an every 3 month basis. Imaging studies, including a chest CT scan (with or without contrast) and an abdominal/pelvic MRI with contrast, will be performed every 12 weeks until the time of disease recurrence, withdrawal of patient consent, or study closure.

5. THERAPEUTIC/DIAGNOSTIC AGENTS

Crizotinib will be taken twice daily at a dose of 250 mg BID, with each dose taken approximately twelve hours apart. Crizotinib will be dosed approximately at the same time each day, and can be dosed without regard to meals. If the patient forgets a dose, they should take it as soon as they remember unless it is less than six hours before the next dose. In that case, they should be instructed to take the next dose. They should not take two doses at the same time to make up for a missed dose. Medication will be dispensed at the beginning of each treatment cycle (28 days) and a pill diary will be used to track adherence. While every effort will be made to encourage medication adherence, missed doses will not be treated as protocol violations unless the number of missed doses is greater than 25% of the total scheduled number of doses. Investigators should reference the current approved prescribing information.

Crizotinib will be provided as capsules containing 200 or 250 mg of study medication for oral administration. The 200 mg and 250 mg capsules are oval in shape. The tablets are packaged in HDPE bottles and should be stored at 15 to 30°C and handled with care.

Crizotinib should be stored at room temperature (15-30° C).

6. CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Primary diagnosis of uveal melanoma at least 12 mm in largest basal diameter as clinically determined by the treating investigator. Cytologic determination of diagnosis is not required. Size is based on clinical assessment (e.g. by ultrasound or direct ophthalmoscopy) prior to enucleation or radiation therapy.

2. Definitive therapy of the primary uveal melanoma must have been performed within 120 days of initiating protocol therapy.

3. High-risk (class 2) uveal melanoma as determined by gene expression profiling (GEP; DecisionDx-UM, Castle Biosciences Inc, Friendswood, TX).

4. No evidence of metastatic disease.

5. Age ≥18 years.

6. ECOG performance status ≤ 1 (Karnofsky ≥ 70%, see Appendix A).

7. Life expectancy of greater than 3 months.

8. Able to swallow and retain orally-administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

9. Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count (ANC) >1,000 cells/mm³
- Platelet count >75,000/mm³
- Hemoglobin >9.0g/dL

- AST and/or ALT <3x upper limited of normal (ULN)
- Total bilirubin <2x ULN
- Alkaline phosphatase <3x ULN

- Serum creatinine <2x ULN or a creatinine clearance > 60mL/min

- Note: Patients with hyperbilirubinemia clinically consistent with an inherited disorder of bilirubin metabolism (e.g., Gilbert syndrome) will be eligible at the discretion of the treating physician and/or the principal investigator.

10. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation until 4 months after completion of crizotinib administration. Women of child-bearing potential must have a negative serum pregnancy test within 14 days prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study therapy, and 4 months after completion of crizotinib administration.

11. Ability to understand and the willingness to sign a written informed consent document.

6.2 Subject Exclusion Criteria

1. History of another malignancy except for those who have been disease-free for 3 years, or patients with a history of completely resected non-melanoma skin cancer and/or patients with indolent secondary malignancies not requiring active therapy, are eligible. Consult the study Principal Investigator if unsure whether second malignancies meet the requirements specified above.

2. Any major surgery or extensive radiotherapy (except that which is required for definitive treatment of primary uveal melanoma), chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 21 days prior to initiation of study therapy.

3. History of prior crizotinib use.

4. Use of other investigational drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of study therapy and during the study.

5. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to crizotinib.

6. Concurrent administration of crizotinib and a strong inhibitor or inducer of CYP3A (see Appendix B) is not permitted. Many over-the-counter and dietary supplements also inhibit or induce CYP3A (see Appendix C for a partial list) and thus are prohibited.

7. A QT interval corrected for heart rate using the Bazett's formula QTcB ≥ 480 msec.

8. Concurrent administration of crizotinib and agents that can cause QTc prolongation (see Appendix B) is not permitted.

9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection, which will be allowed). HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with crizotinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

7. RECRUITMENT PLAN

A member of the patient's treatment team, the protocol investigator or research team at Columbia University Medical Center or Memorial Sloan Kettering will identify potential research participants. If the investigator is a part of the treatment team, s/he will screen the patient as to eligibility, and will discuss the study and the possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be confirmation of the diagnosis of uveal melanoma and ascertaining the exact stage of the disease. Potential subjects that meet these basic criteria will be referred by their treating physician to the investigator/research staff of the study, whether in ophthalmology or medical oncology. The patient will be approached for enrollment on the screening portion of the trial, which will determine risk-stratification by GEP testing. High-risk patients by GEP testing will then be referred to medical oncology, if not previously referred, to discuss the treatment portion of the protocol. The principal investigator will be available to all patients for further questions and information through a contact number which will be provided on the consent form itself.

8. PRETREATMENT EVALUATION

All aspects of the screening evaluation should be completed within 28 days of starting treatment with the exception of scans.

- Documented presence of high-risk (class 2) uveal melanoma as determined by GEP. This may be completed at any time prior to registration.
- Full medical history
- Full medication list

- Standard baseline surveillance imaging with CT scan of the chest (with or without contrast) and MRI of the abdomen and pelvis with contrast up to 60 days prior to starting treatment. CT imaging of the abdomen and pelvic can be substituted for the MRI if indicated.
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight and height. Height may be documented at any time prior to registration.
- 12-lead electrocardiogram (ECG)
- Performance status by KPS or ECOG status (see Appendix A)
- Serum pregnancy test for women with child-bearing potential
- Complete blood count with differential
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST)
- LDH
- Phosphorus

9. TREATMENT/INTERVENTION PLAN

All patients will receive oral crizotinib 250 mg PO BID during the active therapy phase of the study. Dose modifications due to toxicity are described further in Section 11.0. The schedule of evaluations and interventions is described in Section 10.0
The study will be conducted in 3 phases:

1. **Active Therapy Phase:** During the active therapy phase of the study, patients will receive 48 weeks (12 four-week cycles) of crizotinib 250 mg PO BID. Patients will be evaluated by routine bloodwork and physical examination every 4 weeks while they are receiving crizotinib. Imaging studies, optimally including a chest CT scan (with or without contrast) and an abdominal/pelvic MRI with contrast, will be performed at baseline and every 12 weeks.

2. **Follow-Up Phase:** During the follow-up phase of the study, patients will be seen on an every 3 month basis. Imaging studies, optimally including a chest CT scan (with or without contrast) and an abdominal/pelvic MRI with contrast, will be performed every 12 weeks ± 1 week until distant disease recurrence, withdrawal of patient consent, or study closure.

3. **Survival Phase**: Patients who have distant disease recurrence during follow-up will then be contacted every 3 months (+/-2 weeks) to obtain vital status for at least 32 months from the start of active therapy.

10. EVALUATION DURING TREATMENT/INTERVENTION

Evaluations will occur at each clinic visit, which are every 4 weeks (+/- 1 week) for 48 weeks, and every 3 months (+/- 2 weeks) subsequently. Surveillance imaging studies will be performed at baseline and every 12 weeks subsequently (+/- 1 week window). All evaluations and assessments may be performed with a +/- 1 week window unless specified above. The evaluations are delineated further in the study calendar (Table 4)

Quality of life (QoL) will be measured using the Functional Assessment of Cancer Therapy - Melanoma (FACT-M) Version 4 (see Appendix D) to explore potential effect of treatment. The FACT-M consists of 27 items that form four general health subscales: Physical Well-being (PWB), Social Well-being (SWB), Emotional Well-being (EWB), and Functional Well-being. In addition, the FACT-M contains 16 questions which comprise the Melanoma Score (MS). The eight questions from the FACT-M related directly to the melanoma surgery site are excluded for this study since these questions will not be applicable for the patient sample.

In this study, the QoL questionnaire will be administered at baseline, after 4 to 8 weeks of crizotinib therapy, and at the end of the 48 weeks of active treatment. To preclude bias of patient responses by prior knowledge of disease status or other medical outcomes, every effort should be made to administer the QoL questionnaire to patients at their scheduled visits prior to any other assessments, treatment administration, physician/investigator consultation, and prior to being informed of his/her disease status. Upon completion, the investigator, research nurse, or study coordinator should immediately review the questionnaire. This should be done to ensure that every question has been answered and that there is only one response for each question. If omissions or double responses occur, they should be brought to the attention of the patient.

		Active Therapy Phase	**Follow-Up Phase**	**Recurrence visit[k]**	**Survival Phase**
	Pre-Study	**Every 4 Weeks for 48 Weeks**	**Every 3 Months[j]**		**Every 3 Months[l]**
Crizotinib		X			
Informed Consent	X				
Demographics	X				
Medical History	X	X	X	X	
Concurrent Meds	X	X	X	X	
Physical Exam	X	X	X	X	
Vital Signs	X	X	X	X	
Height	X				
Weight	X	X	X	X	
Performance Status	X	X	X	X	
CBC w/ Diff, PLTs	X	X	X	X	
Serum/plasma Chemistry[a]	X	X[b]	X	X	
Serum/Plasma Pregnancy Test[c]	X				

EKG[d]	X	X			
Adverse Event Evaluation[e]	X	X	X	X	
CT and/or MRI Radiographic Imaging[f]	X[f]	Every 12 weeks[f]			
FACT-M Assessment[g]		X			
Tumor Biopsy for GEP[h]	X				
Tumor Biopsy at Time of Progression				X	
Research Blood Collection[i]		X	X	X	
Survival Phone Call					X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Hepatic function panel (Albumin, alkaline phosphatase, total bilirubin, AST, ALT) will be obtained every 2 weeks for first eight weeks, then every four weeks for remainder of 48-week duration.
c: Perform only in women of child-bearing potential.
d: A single 12-lead ECG should be performed at Screening and prior to dosing on Day 1 of each 4-week cycle during the treatment phase. The first treatment-phase EKG does not need to be conducted if the baseline EKG was conducted within 28 days of treatment start date. Additional EKGs will be performed as clinically indicated. Patients with a baseline QT interval corrected for heart rate using the Bazett's formula QTcB ≥ 480 msec are excluded from this trial.
e: Adverse event evaluation should be performed during the active therapy phase and up to 30 days following completion of crizotinib administration. No subsequent adverse event evaluation is required.
f: Surveillance imaging studies will be performed at baseline and every 12 weeks (+/- 1 week window for imaging studies). Every attempt should be made to perform a CT of the chest (with or without contrast) as well as an MRI of the abdomen and pelvis with contrast; however, alternative imaging modalities may be performed upon discussion with the Principal Investigator.
g: The FACT-M questionnaire will be administered at baseline, after 4 to 8 weeks of crizotinib therapy, at the end of active treatment.
h: High-risk (class 2) uveal melanoma as determined by gene expression profiling (GEP; DecisionDx-UM, Castle Biosciences Inc, Friendswood, TX) may have been performed at any time prior to study initiation.
i: Serum will be collected from patients in 4 cell preparation (CPT) tubes with sodium heparin or ACD yellow top tubes (approximately 8 mL/tube) only at baseline, and 1 Streck blood collection tube (BCT) (approximately 8 mL/tube) at baseline, at weeks 4, 8, and 12, and then every 12 weeks thereafter until 132 weeks or recurrence, inclusive. Standard sodium heparin or K3-EDTA tubes can substitute for CPTs or Streck BCTs if necessary.
j: Patients will be evaluated every 3 months (+/- 2 weeks) for follow up assessment until distant disease recurrence, withdrawal of patient consent, or study closure.
k: Patients who do not withdraw consent will have a recurrence visit within 30 days of distant disease recurrence.
l: Patients will be contacted every 3 months (+/-2 weeks) for at least 32 months from the start of active therapy for survival data.

10.1 Correlative Studies

Correlative studies of the primary tumor, peripheral blood, and metastatic samples will be critical to see if a biomarker and possible mechanism can be identified for those responding

or not responding to the therapy.

10.1.1 **Correlative Studies on Primary Tumor**

At diagnosis, an FNA of the primary tumor will be performed and sent to Castle Biosciences for GEP analysis via the DecisionDx-UM test per standard of care. Patients who undergo enucleations may have 5 unstained formalin-fixed, paraffin-embedded slides sent for this test in lieu of an FNA as standard of care. Tumor FNAs and/or enucleation samples performed prior to screening consent (e.g. at an outside institution) may be used for correlative analysis if patients have consented to Castle Bioscience's biospecimen repository.

Should sufficient additional sample be available at Castle Biosciences, RNA expression levels of genes relevant to UM biology, including, but not limited to, HGF,[56,57] MYC,[58] BAP1,[59,60] EGFR,[57] IGF-1R,[57] MITF,[61] SF3B1,[62,63] EIF1AX,[62] DDX43,[64] and STAT3,[65] as well as cMET, ROS, and ALK, all targets of crizotinib, will be assessed by Castle Biosciences. We will set cMET and the other analytes onto an ABI TLDA card using TaqMan assays.

If any fresh frozen, paraffin embedded and/ or cells from tumor tissues is available in excess of that required for pathological diagnosis or for the analysis described above, it may be obtained for additional correlative studies to be performed at each of the participating sites. Tumor FNAs and/or enucleation samples performed prior to screening consent (e.g. at an outside institution) may be used for correlative analysis if patients have consented to other appropriate protocols (e.g the Ohio State University Uveal Melanoma genetics study [IRB#06036]).

10.1.2 **Correlative Studies on Blood**

Patient serum and/or plasma for research purposes will be obtained at baseline before treatment on Day 1, at each on-treatment and follow-up visit, and at the off-study visit.

Four cell preparation tubes with sodium heparin or ACD yellow top tubes (~8 mL/tube) and 1 Streck blood collection tube (BCT) or equivalent (~8 mL) will be obtained at baseline.

While on study, 1 Streck BCT or equivalent will be obtained at Weeks 4, 8, 12, and then every 12 weeks thereafter until 132 weeks or recurrence, inclusive. Standard sodium heparin-containing and/or K3-EDTA tubes can substitute for CPTs and Streck BCT if necessary. These samples will be banked for circulating tumor DNA and companion normal gene expression profiling studies.

Samples will be spun and separated into plasma and cellular components and circulating cell-free (tumor) DNA and cell-associated DNA extracted. At OSU, this will be performed at Dr. Abdel-Rahman's laboratory or the Human Genetics Sample Bank core facility, and

all DNA samples will be logged into the study database so that they can be linked to the individual's unique identifier. Inflammatory studies to assess the role of the immune system in response to crizotinib therapy will be performed at OSU. KIR and HLA allelotyping, germline polymorphism analysis of immune modulating genes, and other analyses will be performed on peripheral blood DNA in Dr. Abdel-Rahman's laboratory at OSU.

Genotyping and sequencing will be assessed by digital PCR for tumor genes including but not limited to GNAQ/11, SF3B1, EIF1AX and BAP1 mutation to assess levels of circulating tumor DNA in response to therapy and compare to cell-associated peripheral blood DNA. Although these studies will be performed in a central study laboratory, additional correlative studies may be performed at each of the participating sites.

10.1.2 **Correlative Studies on Metastatic Tumor**

If and when metastatic disease or recurrence is suspected, at least 3 cores and up to 5 cores from the patient's biopsy specimen will be flash frozen and banked for research purposes. RNA expression levels of the same genes noted above (cMET, HGF, ROS, ALK, MYC etc) will be assessed from these specimens. Follow-up validation studies of these target genes (e.g. protein expression, immunohistochemistry, etc.) will be performed as required from analysis of GEP data. If a total of 5 cores may be safely obtained, 2 fresh cores may also be utilized to establish cell lines, organoids, and/or patient derived xenografts in immunocompromised mice as described below under **section 10.2.3**. Inflammatory marker immunohistochemistry studies for all patients will be performed at OSU. Additional correlative studies may be performed at each of the participating sites.

Every reasonable effort should be made to obtain correlates at each time point, but omitted correlates will not be considered protocol violations and a later time point may substitute for a missed time point.

10.2 **Processing of Samples for Correlative Studies**

10.2.1 **Plasma for cell free DNA**

Plasma for cell-free DNA should complete processing as soon as possible, ideally within 6 hours of collection for EDTA tubes or within 72 hours of collection for Streck BCTs. Tubes should be centrifuged at 820 x G for 10 minutes, with supernatant transferred to 1.5 mL Eppendorf tubes in 1 mL aliquots. A goal of 2 mL plasma should be obtained. The sample should be centrifuged at 1600 x G for 10 minutes at 4^{o}C to pellet any remaining cellular debris, which should be discarded. The supernatant should then be labeled with subject identification number, date, time point (e.g. baseline, week 4), and the name of the center. These samples should be stored at -80^{o}C. Shipments will be sent to the analysis laboratories by batch shipments when possible. The analyzing laboratories will be

notified by email (vialea@mskcc.org) the day the samples are sent.

The email will contain the following information:

- Subject ID
- Subject Initials
- Visit Name
- Date of collection
- Time of collection
- Time of Freezing

All samples should be directed to the address listed on the tissue sample shipment form. Samples should be shipped via courier so that the package is tracked appropriately (specifically Federal Express or UPS).

Specimens will be packed in dry ice in a way to ensure they remain frozen during shipment and do not break. All specimens must be shipped with appropriate identifiers. The samples should be shipped for morning delivery, Monday through Thursday for optimal processing. DNA may isolated locally and shipped directly to CUMC. At OSU circulating cell-free (tumor) DNA extracted at Dr. Abdel-Rahman's laboratory or the Human Genetics Sample Bank core facility at OSU. All DNA samples will be logged into the study database so that they can be linked to the individual's unique identifier. Date and time of collection and freezing will be collected. DNA will be shipped in a batch shipment to the analyzing laboratory.

Samples will be tracked through a Microsoft Excel tracker.

10.2.2 **Blood for PBMC Isolation**

PBMC isolation will be performed at baseline only. Please ensure an absolute lymphocyte count and an absolute monocyte count are collected when PBMCs are obtained so that PBMCs can be quantified.

Invert tubes 8-10 times and store upright at ambient temperature until collection. Label the tubes appropriately. Isolation and freezing should be completed under sterile technique, preferably a biosafety cabinet, and completed within 6 hours of blood collection.

Centrifuge for 20 minutes at 1700 x g. If after centrifugation the upper phase above the gel is not clear of RBCs, the tube should be centrifuged for an additional 15 minutes. After centrifugation, the PBMCs will be found in a diffuse, whitish layer

above the gel or on the sides of the tube. Without disturbing the cell layer, use a transfer pipette to remove approximately half the upper clear plasma layer (~3 mL). With a clean transfer pipette, gently pipette the remaining plasma and cells up and down to dislodge any cells that may be resting on the gel layer, or the sides of the tube. Transfer the cell suspension to a 15 mL conical tube. Add room temperature RPMI-10 to the conical tube to a final volume of 13 mL, cap the tube tightly, and mix by gentle inversion. Centrifuge at 250 × g for 15 min at room temperature. The supernatant may be cloudy. These are platelets above the cell pellet. Decant or aspirate the supernatant without disturbing the cell pellet. Flick the tube to resuspend cells. Repeat washing steps (RPMI-10, suspension, centrifuge, decant supernatant) 1-2 more times. While waiting for the 2nd (or 3rd) wash, fill an insulated ice pan with ice. After the 2nd (or 3rd) wash is complete, remove a small aliquot to record the cell count and viability, then place tube on ice.

For each timepoint, collect the following parameters:

i. Cell viability (%) before freezing
ii. Total yield of PBMCs (x 106 cells/mL/vial) isolated prior to freezing

Prepare a freezing container (e.g. Nalgene cat #5100-0001 or equivalent) Remove the high-density polyethylene vial holder and foam insert from the Nalgene Freezing Container. Do not discard the foam insert. Container must be at room temperature prior to use. Do not pre-chill. Add approximately 250 mL of 100% isopropyl alcohol to the fill line on the Freezing Container. Do not overfill. Carefully replace the foam insert and vial holder in the Freezing Container.

To freeze the PBMCs: Important to Note: PBMC Freezing media contains DMSO, which is toxic to the cells if they are not frozen immediately after suspension in freezing media. Flick 15mL centrifuge tube containing the PBMC pellet to resuspend cells. Using a transfer pipette, quickly resuspend the pellet in 1 mL of COLD Freezing Medium.

i. NOTE: Prepare media per the instructions contained inside the media kit box.

ii. Mix the cells up-and-down a few times until well mixed (no visible clumps).

Immediately dispense the entire volume into the pre-labeled cryovial. Cap the vial tightly. Keep samples on ice until transferred to the Freezing Container. Aliquot PBMCs into provided labeled cryovials. A minimum of seven (7) cryovials should be obtained.

iii. NOTE: Each cryovial should contain a minimum of 5x106 cells/mL/vial and a maximum of 15x106 cells/mL/vial. For each cryovial prepared, please record the total # of PBMCs in the cryovial.

iv. If there are less than 35 million cells, as many cryovials with 5 million cells should be made as possible.

v. Place sample vials in Freezing Container vial holder. Place the lid on the Freezing Container and place in a -70□C/-80°C freezer immediately. For each cryovial prepared, please record the date and time placed into the freezer.

vi. NOTE: Leave undisturbed overnight or for a minimum of 12 hrs and a maximum of 24 hrs.

Transfer samples to liquid nitrogen storage freezer. Record the time, date, and location that the samples were placed in liquid nitrogen storage. For each cryovial prepared, please record the date and time placed into liquid nitrogen storage.

Shipments will be sent to the Schwartz laboratory by batch shipments when possible. The analyzing laboratories will be notified by email (ga2391@columbia.edu) the day the samples are sent.

The email will contain the following information:

- Subject ID
- Subject Initials
- Visit Name
- Date of collection
- Time of collection
- Time of Freezing

All samples should be directed to the address listed on the tissue sample shipment form. Samples should be shipped via courier so that the package is tracked appropriately (specifically Federal Express or UPS). Specimens will be packed in dry ice in a way to ensure they remain frozen during shipment and do not break. All specimens must be shipped with appropriate identifiers. The samples should be shipped for morning delivery, Monday through Thursday for optimal processing.

Samples will be tracked through a Microsoft Excel tracker.

Five micrograms of the DNA isolated from peripheral blood from PBMCs from each patient will be sent in bulk to Dr. Abdel-Rahman's laboratory for KIR and HLA allelotyping and inflammatory SNP analysis. The DNA will be labeled with

the appropriate identifiers and concentration and shipped via courier so that the package is tracked appropriately (specifically Federal Express or UPS). The analyzing laboratories will be notified by email (mohamed.abdel-rahman@osumc.edu) the day the samples are sent.

10.2.3 **Core Biopsy Specimens**

Tissue should be divided such that one core is placed in buffered formalin and paraffin embedded as standard of care for histologic diagnosis of recurrence. Additional core biopsy specimens, if safe to obtain, will be utilized for gene expression and confirmatory protein studies as well as establishment of cell lines and/or patient derived xenografts.

Personalized tumor models consisting of cell lines, organoids, and xenografts, will be created by the Olive Laboratory under IRB protocol AAAR4172. Two fresh cores would be transferred directly from the intervention suite to media appropriate for establishing cell lines, organoids, and/or implantation into mice. These cores will then be delivered to the Olive Laboratory at the address listed below:

Olive Laboratory
Columbia University Medical Center
1130 St. Nicholas Avenue
ICRC Room 217A
New York, NY 10032

Tumor model creation will only be performed for study patients treated and followed at Columbia University Medical Center. All data and specimens shared with the Olive Laboratory will be fully coded unless the patient also consents to IRB protocol AAAR4172 which allows for the collection of clinical data including direct identifiers (in conjunction with the establishment of personalized models).

The remaining tissue should be flash frozen in liquid nitrogen for 2 minutes or longer until frozen solid and then stored at -80^{o}C or below.

Shipments will be sent to the Schwartz laboratory by batch shipments when possible. The analyzing laboratories will be notified by email (ga2391@columbia.edu) the day the samples are sent.

For inflammatory marker immunohistochemistry studies at OSU, five, 5 micron section unstained slides from fresh frozen or archival material of the metastatic liver tissue biopsy will be transferred in bulk shipment to the Abdel-Rahman laboratory. The analyzing laboratory will be notified by email (Mohamed.abdel-rahman@osumc.edu). Fresh-frozen tissue slides will be labeled with appropriate identifiers and packed in dry ice in a way which will avoid breakage. Formalin-fixed specimens may be shipped at room temperature in containers to avoid

breakage.

The email will contain the following information:

- Subject ID
- Subject Initials
- Date of collection

All samples should be directed to the address listed on the tissue sample shipment form. Samples should be shipped via courier so that the package is tracked appropriately (specifically Federal Express or UPS).

Specimens will be packed in dry ice in a way to ensure they remain frozen during shipment and do not break. All specimens must be shipped with appropriate identifiers. The samples should be shipped for morning delivery, Monday through Thursday for optimal processing.

Samples will be tracked through a Microsoft Excel tracker.

11. TOXICITIES/SIDE EFFECTS

Toxicity grading will be performed in accordance with NCI CTCAE, version 4.0. For safety and adverse event reporting, see section 17.0.

11.1 **Dose Modification**

Crizotinib has been studied in multiple phase I to III trials. Side effects of crizotinib that are commonly seen including nausea, vomiting, and visual changes, including floaters, flashes of light, double vision and blurred vision. More uncommon side effects of crizotinib include fatigue, constipation, altered taste, edema, elevated transaminases, dizziness, and anorexia. Rare, but serious side effects include neutropenia, anemia, renal dysfunction, arrhythmias, hypotension, hyponatremia, and pneumonitis. Patients will be monitored closely for toxicity and the dose of crizotinib may be adjusted as suggested in the tables below. Up to 2 dose reductions may be performed. Should further intolerable toxicity occur despite 2 dose reductions, then treatment will be discontinued. Investigators should reference the current approved prescribing information for additional dose modifications.

Dose Level	Dose
0	250 mg BID
-1	200 mg BID
-2	250 mg daily

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic, general (except for what is noted below)*	Continue at same dose level.	Continue at same dose level if tolerable.	Withhold dose until toxicity is grade ≤ 1, then resume treatment at same dose level, or the next lowest dose level, at the discretion of the investigator.	Withhold dose until toxicity is grade ≤ 1, then resume treatment at next lowest dose level.
ALT and/or total bilirubin elevation	For Both: Continue at same dose level.	For ALT: Continue at same dose level For Bili: Withhold dose until toxicity is grade ≤ 1, resume treatment at one dose level reduction. If recurs, then decrease one additional dose level. If no recurrence after 4 weeks, dose can be re-escalated as tolerated.	For ALT: Withhold dose until toxicity is grade ≤ 1, resume treatment at one dose level reduction. If recurs, then decrease one additional dose level. If no recurrence after 4 weeks, dose can be re-escalated as tolerated. For Bili: Discontinue treatment, do not re-treat.	For ALT: Withhold dose until toxicity is grade ≤ 1, resume treatment at one dose level reduction. If recurs, then decrease one additional dose level. If no recurrence after 4 weeks, dose can be re-escalated as tolerated. For Bili: Discontinue treatment, do not re-treat.
Left ventricular systolic dysfunction	Continue at same dose level.	Continue at same dose level.	Discontinue treatment, do not re-treat.	Discontinue treatment, do not re-treat.
Prolonged QTc	Continue at same dose level.	Correct electrolytes, address concomitant medications.	Withhold until at baseline. Correct electrolytes, address concomitant meds, resume treatment at 150mg BID. If recurs, discontinue permanently. If no recurrence after 4 weeks, dose can be escalated to 200 mg BID.	Discontinue treatment, do not retreat.
Pneumonitis (in the absence of other causes of pulmonary infiltrates/dysfunction)	Withhold until at baseline. Resume treatment at same dose. If recurs, discontinue permanently.	Withhold until at baseline. Resume treatment with dose reduction of 1 level. If recurs, discontinue	Discontinue treatment, do not re-treat.	Discontinue treatment, do not re-treat.

		permanently.		
Visual disturbance**	Continue at same dose level. Consider ophthalmology evaluation.	Continue at same dose level. Consider ophthalmology evaluation.	Withhold until at baseline. Refer for ophthalmology evaluation. Resume at 200 mg BID.	Discontinue treatment, do not re-treat. Refer for ophthalmology evaluation.
Hematologic (excluding lymphopenia*)**	Continue at same dose level.	Continue at same dose level.	Withhold until toxicity is grade ≤ 2. Can resume treatment at same dose or reduce dose at 200 mg BID, based on treating physician's discretion.	Withhold until toxicity is grade ≤ 2. Resume treatment at 200 mg BID.

*Grade 4 hyperuricemia or grade 3 hypophosphatemia without symptoms can continue with interruption at the discretion of investigator. Nausea, vomiting or diarrhea must persist at grade 3/4 despite maximal medical therapy, to require dose modification.
** Please see text below regarding reporting requirements for visual disturbances.
***Patients with isolated grade 3/4 lymphopenia, may continue study treatment without interruption.

11.2 **Reporting Requirements for Visual Disturbances**

The U.S. FDA has asked Pfizer to conduct a non-interventional enhanced pharmacovigilance study titled "A Descriptive Study of Potential Sight Threatening/Severe Visual Loss Following Exposure to XALKORI" (Study A8081062). The objective of this study is to evaluate risk factors for, and outcomes of, PST or SVL adverse events among patients with cancer being treated with crizotinib. The study is due to commence on March 31, 2016 and end on March 31, 2021.

In all crizotinib-treated patients, Grade ≥2 PST (except for Visual field defect, for which Grade ≥3 is the standard) or SVL should be treated as Serious Adverse Events, regardless of relatedness to study drug. The following MEDdra preferred terms are considered indicative of a PST or SVL event: Amaurosis, Amaurosis fugax, Blindness, Blindness cortical, Blindness day, Blindness night, Blindness transient, Blindness unilateral, Hemianopia, Hemianopia heteronymous, Hemianopia homonymous, Optic atrophy, Optic ischaemic neuropathy, Optic nerve disorder, Optic neuropathy, Quadranopia, Retinopathy, Sudden visual (or vision) loss, Toxic optic neuropathy, Tunnel vision, Visual cortex atrophy, Visual field defect, Visual pathway disorder, Retinal oedema, Retinal detachment, Maculopathy, Iritis, Uveitis, Visual field test abnormal. The occurrence of Grade ≥2 of any of these events should be treated as a SAE, except for Visual field defect, for which only Grade ≥3 should be treated as a SAE. Grade 2 events are considered to be PST and Grade ≥3 events are considered to be SVL.

These visual SAEs must be reported within 24 hours of you or your staff member becoming aware of them to the CUMC study team as outlined in Section 17 for CUMC patients and

in Appendix D for participating centers. Pfizer will then be immediately notified by the CUMC research team. After the SAE is to Pfizer, a PST/SVL Data Capture Aid (DCA) which contains relevant clinical and diagnostic questions, including information from any ophthalmic examinations, will also be requested. Pfizer Local Drug Safety Unit will contact you to complete the form. If you have any questions regarding SAE information for PST or SVL events, please contact the study PI, Robin Wiltshire at robin.wiltshire@pfizer.com, or Elizabeth Kim at elizabeth.kim@pfizer.com.

12. CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Imaging studies will be conducted to evaluate tumor recurrence as outlined in the study calendar. Additional imaging studies may be performed at the discretion of the investigator. The same method(s) of tumor assessment and the same technique(s) should be used at each radiologic evaluation to confirm that there are no new lesions or to identify and follow any new lesions. At the time of a patient's enrollment in this study, there should be no current radiological evidence of disease. Any clinical or radiographic evidence of recurrence is considered evidence of progression.

When there is radiologic evidence of recurrence, pathologic confirmation should be obtained whenever possible. Other imaging studies may be used in conjunction with the study mandated imaging to help the principal investigator determine whether or not there is true disease progression, although these scans should not replace CT imaging in terms of disease follow-up for this study. If biopsy is not possible and there are indeterminate radiographic findings, repeat imaging studies at a 4 week interval may be performed to confirm recurrent disease.

13. CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. Patients who discontinue treatment early should return within 30 days of the last dose of the study drugs for a follow-up evaluation. Any assessments listed for the final visit in the study calendar will be performed at that time.

Other reasons for study discontinuation include, but are not limited to:

- Non-compliance with the defined treatment plan
- Investigator's decision based on patient's best interest
- Withdrawal of consent
- Severe, unexpected toxicities/side effects
- Lost to follow-up
- Completion of study requirements after being followed for at least 32 months for survival

14. BIOSTATISTICS

We anticipate a total accrual period of 1 to 2 years (accrual rate of 1 to 2 patients per month on the treatment portion of the study) and additional follow-up after the accrual interval of 32 months. Prior data indicate that 40% of all uveal melanoma patients have Class II, high risk tumors. The median relapse free survival of this group of high-risk patients is approximately 32 months. We hypothesize that the addition of crizotinib will increase the 32-month RFS by 25%. Thus, a 32 month relapse free rate of 50% would be considered not promising and a 32 month relapse free rate of 75% or greater would be considered promising. A single stage design based on a binomial probability estimate will be utilized with an alpha of 0.05 and a beta less than of 0.11. This design will require 75 patients to be screened to treat 30 patients. At the end of the study, if at least 20 out of 30 patients are free of distant relapse at 32 months, this adjuvant treatment with crizotinib will be considered worthy of further study. This design yields a 90% probability of a positive result if the relapse free rate at 32 months is at least 75% and a 95% probability of a negative result if the true relapse free rate is 50% at 32 months. In order to account for an estimated 5% dropout rate, 34 patients will be accrued to this study. The first 30 patients who relapse by 32 months or have been followed for 30 months will be included in the analysis.

The median, 1-year, 2-year, and 3-year RFS rates will be assessed. RFS rate will be defined as the percentage of patients who do not experience any new tumor growth at any site on the body distant from the primary site or death from any cause from the time of primary therapy of the uveal melanoma (date of enucleation or day of removal of the radioactive plaque) to the end of the relevant time point. All patients who do not withdraw consent will be contacted for a minimum of three years from start of study treatment for survival data.

Overall survival (OS) will be defined as the time from treatment start to date of death or last followup and estimated using Kaplan-Meier methodology. Disease-specific survival (DSS) is defined as the time from treatment start to death due to disease or last followup. Patients who die from other causes will be censored.

The safety and tolerability of crizotinib will be determined by reported AEs, physical examinations, and laboratory tests. Frequencies of toxicities by grade according to NCI CTC will be tabulated.

The FACT-M total score will be computed as sum of all 27 item scores. Four subscale scores will be derived from the 27 items:

- Physical Well-being (PWB)
- Social Well-being (SWB)
- Emotional Well-being (EWB)
- Functional Well-being (FWB)

From the additional 16 items of the FACT-M questionnaire, a total Melanoma Subscale (MS) score will be derived in the following manner: MS = (sum of non-missing item

scores) multiplied by (16 divided by the number of non-missing items). The total and domain score will be summarized using descriptive statistics (e.g., N, mean, SE, median, minimum, maximum) for each assessment time.

If this clinical trial meets its efficacy endpoint, ≤10 patients will experience disease recurrent by 32 months. Conservatively assuming that 20% of patients will have insufficient material for testing, we will have 8 matched primary/metastatic sample sets for comparison. More samples will be available if the recurrence rate is greater. Given the potentially limited number of matched samples available, this analysis will be hypothesis generating for the development of future studies with larger sample sizes. We will analyze each matched pair for differential gene expression and expression of each gene of interest in all primary and metastatic specimens will be summarized as means +/- standard errors of the means, with statistically significant differences between control and tumor samples assessed by paired t-test.

All patients who receive at least 1 cycle of crizotinib will be considered evaluable for the primary endpoint. Those who discontinue study before 1 cycle is complete will be considered replaceable.

15. RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:
Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line "AAAO8010 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form

- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
  - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
  - Copy of pathology and surgical reports
  - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
  - Protocol deviation/waiver approvals (if applicable)
- **Please note**: subject line of email or fax should include the following: "AAAO8010 Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. .All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

15.2 **Randomization**

N/A

16. DATA MANAGEMENT ISSUES

16.1 **DATA REPORTING / REGULATORY REQUIREMENTS**

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 18.0 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 16.1.3.

16.1.1 **Data Collection**

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

16.1.2 **Data Reporting**

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

16.1.3 **Data and Safety Monitoring Committee**

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee

consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

16.1.4 **Quality Control and Quality Assurance**

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

16.1.4 **Internal On-site Monitoring:**

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

16.1.6 **Confidentiality**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

16.1.7 **Source Documents**

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

16.1.8 **Records Retention**

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.

If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies);
Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

17. SERIOUS ADVERSE EVENT (SAE) REPORTING FOR CUMC

Adverse events

Investigational Agent: Include a comprehensive list of all reported adverse events and any potential risks (such as the toxicities seen with another agent of the same class or risks seen in animals administered this agent) as provided by the manufacturer.

Adverse Event List(s) for Other Agent(s): For each commercial agent, please provide a list of those adverse events most likely to occur on this study, and refer the reader to the

package insert(s) for the comprehensive list of adverse events.

17.1 **Definitions**

Adverse Event:
An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event:
Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalation, unless:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condiction (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
    - social reasons and respite care in the absence of any deterioration in the patient's general condiction
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-

patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Unanticipated Problem:
An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up.

Baseline/Preexisting Condition
A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

17.2 Reporting of Serious Adverse Events

17.2.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

17.2.2 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

17.2.3 Reporting to Drug Manufacturer by Sponsor-Investigator

The Sponsor-Investigator will report to investigational agent manufacturer any serious adverse events within 24 hours of becoming aware of it on the Pfizer Investigator-Initiated Research Serious Adverse Event (IIR SAE) Form/HICCC DSMC SAE Form and submitting with the Pfizer-provided ***Reportable Events Fax Cover Sheet***, so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

If the SAE is fatal or life-threatening (i.e., causes an immediate risk of death)- regardless of the extent of the available information, the SAE must be reported immediately upon awareness.

SAEs will be reported to Pfizer from the time the subject receives the first dose of study drug through and including 28 calendar days after last administration of the study drug. Any SAEs that occur after completion of the reporting time period as defined above are reportable to Pfizer if the Investigator suspects a causal relationship between the Pfizer product and the SAE.

18. INFORMED CONSENT PROCEDURES

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the

study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

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APPENDIX A:

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B:

SUBSTANCES PROHIBITED DURING CRIZOTINIB ADMINISTRATION

CYP3A4 Inhibitors:

- itraconazole, ketoconazole, miconazole, voriconazole
- amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir
- ciprofloxacin, clarithromycin, diclofenac, doxycycline, enoxacin, imatinib, isoniazid, ketamine nefazodone, nicardipine, propofol, quinidine, telithromycin

CYP3A4 Inducers:

- aminoglutethimide, primidone, rifabutin, rifampin, St. John's wort
- carbamazepine, nevirapine, oxcarbazepine, rifapentine
- fosphenytoin, pentobarbital, phenobarbital, phenytoin

Agents with Proarrhythmic Potential

- quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide
- erythromycins, clarithromycin
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

APPENDIX C:

PARTIAL LIST OF SUPPLEMENTS PROHIBITED DURING CRIZOTINIB THERAPY

- Agaricus
- Aloe Vera
- Black Cohosh
- Chrysanthemum
- Echinacea
- Elderberry
- Epimedium
- Garlic
- Ginseng
- Goldenseal
- Grape Seed extract
- Green Tea extract
- Guggul
- Hawthorn
- Hoodia
- Licorice
- Milk Thistle
- Mistletoe
- Noni
- Nigella sativa
- Quercetin
- Resveratrol
- Rhodiola
- Sho-saiko-to
- St. John’s Wort
- Turmeric
- Valerian
- Check with your doctor before taking any over the counter or other dietary supplements.

APPENDIX D:

GUIDELINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

1. Multi-site Communication:

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate, at minimum, regularly scheduled conference calls with affiliate sites.

The following issues will be discussed, as appropriate:

- Enrollment information
- Cohort updates (e.g., DLTs)
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

2. New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

3. Regulatory Documents:

Prior to Site Initiation:

Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)

- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to AAAO8010@columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

4. Site activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

5. Central Registration Procedures- Affiliate Institution Research Participant Registration Process:

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's designee (CUMC's study specific Clinical Research Coordinator or Clinical Research Nurse). The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email at AAAO8010@columbia.edu (or via fax at 212.305.5292), with a request to register the patient "pending eligibility." The title of the email should read, "AAAO8010 Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:

a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
b. Redacted Signed HIPAA (or institutional equivalent)
c. MCT CPDM Velos Note to File form

2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC's study specific Clinical Research Coordinator or Clinical Research Nurse) via telephone or email to communicate the following:
   - Notify of pending registration request
   - Confirm method of registration request submission (email or fax)
   - Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)

3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC study specific designee:
   - A signed Affiliate Site Eligibility Checklist (signed by the investigator)
   - Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
     - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
     - Copy of pathology and surgical reports
     - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
     - Protocol deviation/waiver approvals (if applicable)
   - **Please note**: subject line of email or fax should include the following: "AAAO8010 Complete Subject Registration Request (PHI)".

4. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

5. Upon receipt of the subject registration notification email, the CUMC study specific designee will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

6. All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

6. Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB eligibility deviation approval letter(s) should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation and registering/enrolling the subject via CUMC Central Registration. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described.

7. Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

    a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is

responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

MCT Remote Monitoring:

1. When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.

2. Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.

3. Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case by case basis.

4. The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.

5. The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.

6. The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:

    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance

d. Protocol specific toxicity/outcome documentation/compliance
e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
g. Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
h. Pharmacy accountability records
i. Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)

7. Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

8. Dose Level Determinations:

The sponsor-investigator will review enrollment for each dose level cohort during the regularly scheduled conference call with the affiliate sites.

The dose level for newly enrolled subjects will be determined by the study statistician upon notification that a subject has signed informed consent to participate in the study. The assigned dose level for any subject to begin study treatment will be communicated to the affiliate site along with the determination by Central Registration that the subject is eligible for enrollment in the study.

If a Dose Limiting Toxicity (DLT) is identified in a subject, the affiliate site must notify the sponsor-investigator via email at the study specific email address within 1 business day of identification. The lead site will communicate that a DLT has been experienced within 1 business day.

9. Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting

Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Richard Carvajal, M.D.
177 Fort Washington Avenue
Suite 6-435
New York, NY 10032
AAAO8010@columbia.edu

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow- up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject **continued** or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB) and the Data and Safety

Monitoring Committee:

All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.

Expected AEs must be reported at the time of continuing review of a protocol.

Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

Reporting to Hospital Risk Management

Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

10. Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations

outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier. If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

11. Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

12. Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

13. Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each

individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.