UCSF Helen Diller Family Comprehensive Cancer Center

NCT# 02587650

PHASE II TRIAL OF TARGETED KINASE FUSION INHIBITION IN UNRESECTABLE STAGE III/IV BRAF/NRAS WILD-TYPE MELANOMA

Protocol Number: CC #14859
Study Drug: Capmatinib, Ceritinib, Regorafenib, Entrectinib

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

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Printed Name

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Signature Date

Principal Investigator **Site**

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Abstract

Title	Phase II trial of targeted kinase fusion inhibition in unresectable stage III/IV BRAF/NRAS wild-type melanoma
Patient population	Patients with metastatic melanoma who are wild-type (WT) status for BRAF, NRAS, and who also have an oncogenic kinase fusion.
Rationale for Study	BRAF WT melanoma patients currently have no options for molecularly targeted therapy. Given the low response rate to currently approved immunotherapies, there is a need for more therapeutic options in patients with BRAF/NRAS WT metastatic melanoma.
Primary Objective	• To estimate the clinical activity of tyrosine kinase inhibitors matched to the activated kinase fusion partner in patients with metastatic melanoma.
Secondary Objectives	• To estimate tumor stability in kinase fusion melanoma patients treated with kinase inhibitors matched to the activated fusion partner. • To estimate survival in kinase fusion melanoma patients treated with kinase inhibitors matched to the activated fusion partner. • To examine the safety and tolerability of kinase inhibitors in patients with the kinase fusion targets.
Exploratory Objectives	• To explore molecular mechanisms of resistance for patients who progress on therapy.
Primary Endpoint	• Confirmed ORR by RECIST v1.1 at 24 weeks.
Secondary Endpoints	• Confirmed CBR (defined as CR or PR or SD for >24 weeks). • Determination of PFS and OS. • Evaluation of the adverse effect profile, using CTCAE v4.03, of each kinase inhibitor.
Exploratory Endpoints	• Exploratory endpoints to include assessment of expression levels of the fusion kinase protein, reported as percentage by IHC staining. Measures taken at baseline and after 4 weeks of therapy will be summarized. Changes in expression level will be assessed between baskets using a paired t-test if data permit. For patients who progress on therapy, an additional biopsy may be obtained and will be compared with baseline expression levels if data permit.
Study Design	This is a phase II multi-center prospective basket trial designed to test the hypothesis that targeting specific kinase fusions in metastatic melanoma with pre-specified kinase inhibitors will result in objective tumor shrinkage and durable response. The study design is a 2 stage optimal design with a sample size of N=35, with n1=11 during stage I and n2=24 during stage II. If 1 or fewer responses are observed during stage I, the trial will be stopped. If 6 or fewer responses are observed by the end of stage II, the trial will be stopped.

Number of patients	Estimating a drop-out rate of 20%, we anticipate enrolling 44 patients to accrue 35 evaluable patients.
Study Drugs	Capmatinib, Entrectinib, Ceritinib, Regorafenib
Safety Assessments	Physical exam with evaluation of vital signs, performance status, and toxicity grading as per CTCAE v4.03. Clinical laboratory evaluations including CBC, CMP.
Efficacy Assessments	ORR and CBR to be assessed as per RECIST v1.1 criteria.

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
CBC	complete blood cell (count)
CBR	clinical benefit rate
CR	complete response
CRC	Clinical Research Coordinator
CRC	Colorectal Cancer
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FIH	First in Humans
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	Hepatitis B core antibody
HBeAg	Hepatitis B “e” antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HFSR	hand foot skin reaction
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IC50	concentration resulting in 50% inhibition
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product

List of Abbreviations

IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
LLN	lower limit of normal
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ONJ	osteonecrosis of the jaw
ORR	overall response rate
OS	overall survival
PD	disease progression
PFS	progression free survival
PK	pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell (count)
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio

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1 Introduction

Melanoma

Melanoma is the deadliest of all skin cancers, with an incidence rate that is rising worldwide. It is estimated that in 2013, in the US alone, over 80,000 cases of melanoma were diagnosed and over 8,000 patients died of this disease[1]. Fortunately, recent advances in immunotherapy have led to the development of several new agents for metastatic melanoma: the FDA-approved ipilimumab and pembrolizumab, as well as promising PD-L1 antibodies. Another major advancement in melanoma therapy has been in the field of molecularly targeted therapy: BRAF inhibitors with/without MEK inhibitors were recently shown to have benefit in patients whose tumors harbor BRAF mutations[2–4].

While 40-50% of cutaneous melanomas have activating BRAF mutations[5], there remains a sizable BRAF wild type (WT) subset of melanoma that still lacks effective molecularly-targeted therapy options[6]. While 30-40% of patients respond to currently approved immunotherapies, many patients with BRAF WT metastatic melanoma are in need of more treatment options[7,8]. The major subsets among BRAF WT are currently recognized as those with a mutation of NRAS [9,10] as a molecular driver (15-20% across all primary sites except ocular) and those which test WT for both BRAF and NRAS[6].

1.1 Fusion Kinases in Melanoma

Targeting fusion Kinases

There is emerging data that a subset of cutaneous melanomas without mutations in BRAF, NRAS, KIT, GNAQ[11] or GNA11 [12] feature activating kinase fusions. We recently discovered in melanocytic neoplasms including melanomas without these mutations the presence of fusions involving the kinases ROS1 (17%), NTRK1 (16%), ALK (10%), BRAF (5%), RET (3%) and MET [13,14]. The kinase fusions occurred in a mutually exclusive pattern and invariably fused the kinase domains of the respective genes to a variety of N-terminal fusion partners. We showed that the chimeric fusion kinases are enzymatically active and act as constitutively activated drivers of multiple oncogenic signaling pathways. Importantly, cognate kinase inhibitors can inhibit these pathways.

Determination of Specific Kinase Fusions

Identification of kinase fusions can be performed by various methods and is offered by different CLIA laboratories. A separate study protocol aimed at determining the frequency of kinase fusions in BRAF WT melanoma will provide testing through a UCSF CLIA laboratory and report potentially actionable results to the patient's clinician. In this study protocol, fusion kinase detection will be performed using a validated targeted next-

generation sequencing platform. Additional methods that may be employed include fluorescence in situ hybridization and immunohistochemistry. We expect most eligible patients for this study to be tested by the UCSF CLIA laboratory, however, we will accept confirmation of a kinase fusion after review of the test results from other CLIA approved laboratories (i.e. Foundation Medicine)..

1.2 Kinase Inhibitors

Capmatinib (INC280)
INC280 is an ATP-competitive, reversible inhibitor of the c-MET receptor tyrosine kinase. INC280 is highly selective for c-MET (IC50 value of 0.13 nM) as compared to a panel of 56 other human kinases tested. In pre-clinical models, INC280 was shown to have activity against a c-MET amplified gastric cancer cell line (GTL-16) and a c-MET amplified HCC cell line (HCCLM3). Over three phase I trials, 161 patients have been treated with various doses of INC280 with 2.2-8.1% of patients experiencing dose-limiting toxicities. The most common adverse effects were diarrhea, nausea, and vomiting. INC280 is still being evaluated in multiple Phase I and II studies.

Ceritinib
Ceritinib is an ATP-competitive, piperidine tyrosine kinase inhibitor with 20 times the potency against ALK compared to crizotinib (IC50 value of 0.15 nM compared to 3 nM). Ceritinib also has inhibitory activity against INSR and IGF1R, though 50-fold less potency than for ALK (IC50 values of 7 nM and 8 nM, respectively[21]. In pre-clinical models, ceritinib was shown to have activity against crizotinib-resistant ALK-positive NSCLC. In a phase I clinical trial, 59 patients with ALK-rearranged malignancies were enrolled[22]. The maximum tolerated dose was 750 mg once daily. Dose limiting toxicities included diarrhea, vomiting, elevated AST/ALT, and hypophosphatemia. Among 140 patients, the overall response rate was 58%. In eighty patients who had progressed on crizotinib, ORR was 56%. Amongst patients who received at least 400 mg of ceritinib per day, the median progression free survival was 7 months and the median duration of response was 8.2 months. Additionally, ceritinib was shown to have activity against CNS lesions in patients who had progressed on prior therapy with crizotinib.

Ceritinib was granted accelerated approval by the FDA in April 2014 for the treatment of ALK-positive, metastatic NSCLC with disease progression on or who are intolerant of crizotinib. The phase I study (CLDK378X2101) is ongoing; enrollment has been completed in the expansion phase with interim data presented at ASCO 2014. Based on a clinical trial of 163 patients with metastatic ALK-positive NSCLC, treatment with ceritinib resulted in an ORR of 54.6% with a median duration of response of 7.4 months. The complete response (CR) rate was 1.2% and the partial response (PR) rate was 53.4%[23].

Regorafenib
Regorafenib is a carboxamide BRAF and CRAF kinase inhibitor initially developed to target VEGF driven xenografts. This compound also inhibits multiple transmembrane and intracellular kinases RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Eph2A, CRAF, BRAF, $BRAF^{V600E}$, SAPK2, PTK5, and Abl[24]. Regorafenib was recently approved for use in metastatic CRC based

on a placebo controlled Phase III clinical trial[25]. The median overall survival was prolonged from 5 months in the placebo group to 6.4 months in the regorafenib group. The median PFS was similar and response rates were similar. The safety profile of regorafenib is typical of the VEGF inhibitors and includes asthenia/fatigue, decreased appetite and food intake, hand-foot skin reaction, diarrhea, mucositis, weight loss, infection, hypertension and dysphonia. Regorafenib has also been shown to provide significant improvement in PFS compared with placebo in patients with metastatic gastrointestinal stromal tumor (GIST), and is now an approved treatment for GIST[26,27]. We have additional data that BRAF fusion melanoma cell lines are more sensitive to regorafenib and sorafenib, both class II BRAF inhibitors, than to vemurafenib, a class I BRAF inhibitor ([14] and unpublished data, Bastian BC).

Entrectinib (RXDX-101)
Entrectinib is a potent inhibitor of the tyrosine kinases encoded by genes NTRK1, NTRK2, NTRK3, ROS1 and ALK, with IC50 values for kinase inhibition <=12 nM. In pre-clinical models, entrectinib has demonstrated concentration-dependent inhibition of Trk, ROS1, and ALK phosphorylation in cell-based assays using tumor cell lines. It has also demonstrated dose-related antitumor effects in a variety of human tumor xenograft and allograft models dependent on Trk, ROS1, or ALK oncoproteins: namely, anaplastic large cell lymphoma, and intracranial non-small cell lung cancer (NSCLC). Importantly, entrectinib has also exhibited potent antitumor activity both in vitro and in vivo against ALK mutants known to be resistant to the ALK inhibitor crizotinib, thus suggesting that entrectinib has the potential to treat patients with brain metastases and those who have crizotinib-refractory disease. Entrectinib was evaluated in two Phase 1 clinical studies (Study ALKA-372-001 and Study RXDX-101-01 [STARTRK-1]) designed to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of entrectinib in patients with advanced or metastatic solid tumors harboring NTRK1/2/3, ROS1, or ALK molecular alterations. Doses tested ranged from 100 to 1200 mg/m^2, under fasted and fed conditions in both intermittent and continuous daily dosing regimens. Two DLTs were observed: one event of Grade 3 cognitive impairment and one event of Grade 3 fatigue. Both events were reversible upon study drug interruption. Based upon these two DLTs, 400 mg/m^2 administered once-daily on a fed regimen was selected as the BSA-based RP2D. Subsequently, additional expansion cohorts of patients were enrolled to further explore a fixed daily dosing regimen, and 600 mg/day was selected as the RP2D.

1.3 Rationale for the Proposed Study

Current effective treatments for melanoma include immunotherapy and targeted molecular therapies. However, not all patients respond to immunotherapy, and currently approved targeted molecular therapy is indicated only for patients with activating BRAF mutations. Recently, fusion kinases have been identified in melanoma that are mutually exclusive with activating mutations in BRAF. In other cancers, inhibition of similar fusion kinases with kinase inhibitors have demonstrated clinical efficacy. We propose a study of a specific kinase inhibitor for patients with metastatic kinase fusion melanoma. Given that patients with kinase fusion melanomas are a rare cohort without extensive FDA-approved treatment options, they stand to derive great benefit from promising novel agents in melanoma. Patients eligible for this study will be those with melanomas that are BRAF/NRAS wild-type and that have an oncogenic kinase fusion, and who have received at least one FDA-approved line of therapy for unresectable/metastatic

melanoma. Patients who are treatment-naïve but who refuse available standard options and prefer to enroll on study as their first line of treatment after a thorough informed consent process will be eligible for this study at the discretion of the treating physician.

1.4 Correlative Studies

The presence of one of the following integral biomarkers will need to be established by tumor biopsy to establish trial eligibility: oncogenic kinase fusion involving ALK, BRAF, MET, NTRK, RET, or ROS1. Patients will be consented for two biopsies: one biopsy after cycle 1, and one biopsy at the time of progression (if applicable).

Punch or core biopsy is mandatory for easily accessible sites (i.e., palpable, cutaneous, or subcutaneous lymph nodes or lesions). All other lesion biopsies (i.e., lung, liver) that pose more than minimal risk are optional and will be determined by the treating Investigator. Correlative studies to be performed on tumor biopsy specimens will include immunohistochemical assessment of fusion kinase expression levels and activation status.

2 Objectives of the Study

2.1 Primary Objective

- To estimate the clinical activity of tyrosine kinase inhibitors matched to the tumor-specific fusion kinase in patients with metastatic melanoma.

2.2 Secondary Objectives

- To estimate tumor stability in melanoma patients treated with kinase inhibitors matched to the tumor-specific fusion kinase.
- To estimate survival in melanoma patients treated with kinase inhibitors matched to the tumor-specific fusion kinase.
- To examine the safety and tolerability of kinase inhibitors in patients with melanoma with a fusion kinase.

2.3 Exploratory Objectives, Other Assessments

- To explore molecular mechanisms of resistance for patients who progress on therapy.

3 Endpoints of the Study

3.1 Primary Endpoint

- Overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 at 24 weeks.

3.2 Secondary Endpoints

- Clinical benefit rate (CBR) (with clinical benefit defined as complete response (CR) or partial response (PR) or stable disease (SD) for >24 weeks).
- Determination of progression-free survival (PFS) and overall survival (OS).
- Evaluation of the adverse effect profile of each kinase inhibitor, using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

3.3 Exploratory Endpoints

- Exploratory endpoints to include assessment of expression levels of the fusion kinase protein, before and during treatment, reported as percentage by immunohistochemistry (IHC) staining.

4 Study Design

4.1 Characteristics

This is a phase II prospective multi-center basket trial designed to test the hypothesis that targeting specific kinase fusions in metastatic melanoma with kinase inhibitors matched to the activated kinase fusion will result in tumor response. The study design is a 2-stage optimal design. Patients with a eligible kinase fusion in their melanoma, as identified by a CLIA-approved laboratory (targeted next-generation sequencing of tumor tissue, fluorescence in situ hybridization and immunohistochemistry) will be offered enrollment in this protocol and will be treated in one of five baskets. As testing for fusion kinases is not currently part of the standard of care for melanoma, a separate protocol will provide screening for kinase fusions for patients with BRAF wild-type melanoma in a CLIA-approved laboratory at UCSF. Based on the kinase fusions identified, patients will be stratified as follows:

Table 1. Kinase Fusion and Assigned Drug

MET fusion	Capmatinib 400 mg PO BID
ALK fusion	Ceritinib 450 mg PO q day (with low-fat meal)
RET fusion	Regorafenib 160 mg PO q day (first 21 days of each 28 day cycle)
BRAF fusion	Regorafenib 160 mg PO q day (first 21 days of each 28 day cycle)
NTRK1 fusion NTRK2 fusion NTRK 3 fusion	Entrectinib 600 mg PO q day
ROS1 fusion	Entrectinib 600 mg PO q day

The dose of capmatinib at 400 mg PO BID is based on the recommended phase II dose (RP2D) by Novartis. Ceritinib at 450 mg PO daily with a low-fat meal (approximately 100-500 calories, 1.5-15 grams of fat) demonstrated comparable AUC_{0-24h} and C_{max} at Cycle 2 Day 1 to patients treated with ceritinib 750 mg under fasting conditions (the FDA-approved dose for ALK-rearranged NSCLC resistant to intolerant to crizotinib). Both ceritinib dosing regimens showed similar rates of AEs but GI related AEs and dose interruptions were fewer with dosing at 450mg PO daily with a low-fat meal, and for this reason is the chosen dosing. For regorafenib we will dose at 160 mg PO daily (first 21 days of each 28 day cycle) which is the FDA-approved dose for both colon cancer and GIST. The dose of entrectinib at 600 mg PO QD is the RP2D based on two Phase 1 studies conducted by Ignyta. Please refer to Table 1 for drug assignments and Table 2 for drug dose regimens.

4.2 Number of Subjects

We anticipate enrollment of 35 evaluable patients to this study. Identification of a fusion kinase is required for eligibility and testing for fusion kinases is not standard of care. A separate UCSF research protocol will screen melanoma patients in need of treatment who are wild-type for BRAF mutation for fusion kinases (PI: Boris Bastian).

The sample size is based on a 2-stage Simon's optimal design using ORR at 24 weeks as primary efficacy endpoint. We assume that a response rate of 10% would be unacceptable and a response rate of 30% would be considered clinically meaningful. Under type I error of 0.05 and type II error of 0.15, in the first stage of this design, 11 patients will be accrued. If 1 or fewer patients achieve a response among the initial 11 patients, the trial will be terminated. If at least 2 patients achieve a response among these 11 patients, then an additional 24 patients will be accrued to the second stage. If 6 or fewer patients achieve a response, then the trial will be terminated. Under these conditions, if the response rate is 0.1, the probability of ending the trial during stage 1 is 0.70. If the true response rate is 0.3, the probability that the trial will be stopped in stage I is 0.11.

If 35 evaluable patients with follow-up of at least 12 months are enrolled, but fewer than 5 patients are assigned to a given drug, the study will continue to enroll patients until we have enrolled at least 5 patients for each of the 4 study drugs with a max of 50 patients enrolled.

We anticipate enrollment of 35 evaluable patients to this study. Evaluable patients would be those with baseline staging, treatment for at least 8 weeks, and at least one post-baseline staging scan while on treatment. We estimate a drop-out rate of 20%, and therefore 44 patients will be enrolled and started on treatment. Kinase fusion melanoma prevalence is currently estimated at 10% of BRAF/NRAS WT melanomas, thus we anticipate screening 440 patients to enroll 44 patients.

4.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.3.1 Inclusion Criteria

Patients eligible for this study will be those with melanomas that are BRAF/NRAS wild-type and that have an oncogenic kinase fusion. Patients who have received at least one

FDA-approved line of therapy for unresectable/metastatic melanoma are eligible. Patients who are treatment-naïve but who refuse available standard options and prefer to enroll on study as their first line of treatment after a thorough informed consent process will be eligible for this study at the discretion of the treating physician.

Further inclusion criteria vary depending on the basket to which the patient will be assigned. Please refer to the drug-specific appendices for further details on inclusion criteria.

- For patients with MET fusion to be treated with capmatinib, see Appendix 6, Section 6.1.
- For patients with ALK fusion to be treated with ceritinib, see Appendix 7, Section 7.1.
- For patients with RET or BRAF fusion to be treated with regorafenib, see Appendix 8, Section 8.1.
- For patients with NTRK1, NTRK2, NTRK3, or ROS1 fusion to be treated with entrectinib, see Appendix 9, Section 9.1.

4.3.2 Exclusion Criteria

Exclusion criteria vary depending on the basket to which the patient will be assigned. Please refer to the drug-specific appendices for further details on exclusion criteria.

- For patients with MET fusion to be treated with capmatinib, see Appendix 6, Section 6.2.
- For patients with ALK fusion to be treated with ceritinib, see Appendix 7, Section 7.2.
- For patients with RET or BRAF fusion to be treated with regorafenib, see Appendix 8, Section 8.2.
- For patients with NTRK1, NTRK2, NTRK3, or ROS1 fusion to be treated with entrectinib, see Appendix 9, Section 9.2.

4.4 Duration of Therapy

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The Investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject of if the subject cannot comply with the protocol. In addition, any of the following conditions require discontinuation of the subject from study treatment:

- Disease progression.
- An AE or inter-current illness that in the opinion of the Investigator warrants the subject's withdrawal from study.

- If the subject does not recover from his or her toxicities to tolerable Grade ≤2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity.
- Inability to tolerate the lowest dose of study drug as detailed in Table 2.
- Women who become pregnant or are breastfeeding.
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male or female condom) during the course of the study and for 4 months after discontinuation of study treatment.
- Necessity for treatment with other anti-cancer treatment prohibited by protocol.
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol.
- Significant patient non-compliance with protocol.

4.5 Duration of Follow Up

Patients will be followed until death or removal from study, whichever occurs first.

5 Study Drugs

- Capmatinib – See Appendix 6
- Ceritinib – See Appendix 7
- Regorafenib - See Appendix 8
- Entrectinib – See Appendix 9

5.1 Drug Accountability

The Investigational Pharmacist will manage drug accountability records. Accurate records of receipt of all study drugs will be kept, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is being dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study drug will be reconciled and destroyed in accordance with applicable state and federal regulations.

5.2 Drug Ordering

UCSF will obtain capmatinib, ceritinib, regorafenib and entrectinib directly from their respective pharmaceutical companies as study supply.

5.3 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

6 Treatment Plan

Patients will be treated with an appropriate kinase inhibitor as outlined in Table 1. Cycle length is defined for this study as 4 weeks. Patients will be restaged every 2 cycles (8 weeks), and best objective response will be confirmed using RECIST v1.1 with measurements at a minimum of 4 weeks after the response-defining determination. Dose reductions and dose interruptions for management of toxicity will be specified in the sections below.

6.1 Dosage and Administration

Treatment will be administered on an outpatient basis. See Table 2 for dosage and administration information.

Table 2. Drug Regimens

Study Drug	Precautions	Start Dose	Dose Level –1	Dose Level –2	Dose Level –3	Route	Schedule	Cycle Length
Capmatinib	Do not take with food (do not eat at least 1 hour before or 2 hours after drug ingestion)	400 mg	300 mg	200 mg	N/A	PO	BID	28 days
Ceritinib	Take with low-fat meal	450 mg	300 mg	150 mg	N/A	PO	Once daily	28 days
Regorafenib	Take each morning with a low-fat breakfast	160 mg	120 mg	80 mg	N/A	PO	Once daily (21 days on, 7 days off)	28 days
Entrectinib	Take within 1 hour following a meal	600 mg	400 mg	200 mg	N/A	PO	daily	28 days

7 Study Procedures and Observations

7.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section. Screening assessments must be performed within 30 days prior to the first dose of investigational product except for the staging which can be done 90 days prior. Any laboratory results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ± 7 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation. Additional follow-up visits may be added and additional tests ordered per discretion of treating Investigator.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

7.1.1 Pretreatment and Treatment Period

In addition to the assessments outlined in the study calendars, the following will be performed within 30 days before the Day 1 visit.

- Documentation of measureable disease
- History of prior treatments and any residual toxicity relating to prior treatment
- Determination of baseline medications taken within 30 days of Day 1
- Serum Hepatitis assessment, including Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), Hepatitis C antibody
- Serum HIV test

7.1.2 Long Term/Survival Follow-up Procedures

Follow-up history to be conducted by phone call, otherwise per standard of care for metastatic melanoma and PI discretion.

7.1.3 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

8 Reporting and Documentation of Results

8.1 Evaluation of Efficacy (or Activity)

Evaluation of efficacy to be assessed by ORR and CBR, using RECIST v1.1 criteria.

Response and progression in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee[28]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria. Local review of response or progression will be performed at each site. Data for each patient with a response will be reviewed at UCSF.

Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy (with at least 90% of intended dosing administered during cycle 1), and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Disease Parameters

Measurable disease

Measurable disease is defined as the presence of at least one measurable lesion by radiographic assessment or by clinical examination (e.g., skin lesion). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. Positive bone scans and radiographic studies of bone involved with tumor are not considered to be measurable disease.

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). Bone lesions may be measureable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20mm with conventional techniques or < 10mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI

These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

8.1.1.1 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD)

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum LD since the treatment started. Patients having a documented response with no reconfirmation of the response will be listed with stable disease.

Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of “non-target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 3. Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	> 4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	> 4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once > 4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

The best overall response for an early death, i.e., a patient who dies without documentation of disease progression and before it was time to conduct the first tumor reassessment, will be considered inevaluable or not assessed adequately. Response will also be considered inevaluable for any patient receiving treatment (regardless of how much was received) who did not have any follow-up assessment completed before initiation of alternative treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be imaged by PET scan or be investigated by fine needle aspirate/biopsy before confirming the complete response status.

Duration of Response

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.03 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events.

For multicenter studies, the Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

8.3 Definitions of Adverse Events

8.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

8.3.2 Adverse Reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

8.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

8.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema

observed with the drug under investigation should be considered *unexpected* for reporting purposes.

8.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

8.4 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.03.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

8.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

8.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events beginning at the time of informed consent and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer Appendix 4 Multicenter Institutional Studies.

8.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Institutional Review Board (IRB)

The Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Pharmaceutical Companies providing Study Drug

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). As soon as an Investigator becomes aware of an AE that meets the definition of "serious", this should be documented to the extent that information is available. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours. Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the study drug (or therapy) is suspected.

Investigator shall notify the appropriate pharmaceutical company **within twenty-four (24) hours** of making such discovery by submitting the completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form. Applicable events will be reported to the IRB and FDA as per current policies.

This report must be submitted by Institution to the appropriate pharmaceutical company even if it is not felt to be drug related:

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
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  - [redacted]
  - [redacted]

- For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.
- Pregnancy (for a subject or for the partner of a subject) that occurs during study participation, although not itself an SAE, should be reported. To ensure patient safety each pregnancy must also be reported to the appropriate pharmaceutical company within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

SAEs that must be recorded on an SAE Reporting form include the following:

- all SAEs that occur after informed consent and through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure);
- any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the decision to discontinue study treatment;
- although most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
    - elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral hernia repair);
    - pre-specified study hospitalizations for observation; or
    - events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

9 Statistical Considerations and Evaluation of Results

This is a phase II, prospective, multicenter, single arm trial to test the hypothesis that targeting specific kinase fusions in melanoma with pre-specified kinase inhibitors will result in objective tumor response. Patients will be screened for one of the eligible fusion proteins under a separate protocol, and if identified will be treated in this study in one of six baskets (ALK, NTRK, ROS1, RET, MET, or BRAF kinase fusions). The primary endpoint is composite (all fusion types analyzed together) confirmed objective response as defined as a complete or partial response as per RECIST v1.1 criteria. Standard therapies such as IL-2 and ipilimumab have shown response rates of approximately 10%. The newly approved immunotherapy pembrolizumab has a response rate of approximately 30%.

A 2-stage optimal design will be employed in which a 10% response rate is considered not promising, a 30% response rate is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.05 and 0.1, respectively. In this scenario, the maximum trial size would be 35 evaluable patients. Evaluable patients would be those with baseline staging, treatment for at least one cycle (with at least 90% of intended doses administered during cycle 1), and at least one post-baseline staging scan while on treatment. We estimate a drop-out rate of 20%, and therefore 44 patients will be enrolled and started on treatment. In the first stage of this design, 11 patients will be accrued. If 1 or fewer patients achieve a response among the initial 11 patients, the trial will be terminated. If at least 2 patients achieve a response among these 11 patients, then an additional 24 patients will be accrued to the second stage. If 6 or fewer patients achieve a response in the second stage, the trial will be terminated. Under these conditions, if the response rate is 0.1, the probability of ending the trial during stage 1 is 0.70. If the true response rate is 0.3, the probability that the trial will be stopped in stage I is 0.11.

Analysis of study results will be carried out by the study statistician and will include overall response rate (ORR) estimations of ALK, NTRK, ROS1, RET, MET, and BRAF rearrangement-positive patients.

Clinical benefit rate (CBR) defined as the proportion of patients achieving a complete response (CR) or partial response (PR) or stable disease (SD) for > 24 weeks will be estimated for each arm along with a 95% confidence interval.

Progression free survival (PFS) defined as the time from treatment start to the progression or death and overall survival defined as the time from treatment start to death will be estimated using Kaplan-Meier methodology.

Frequencies of toxicities will be tabulated according to CTCAE v4.03 to assess drug safety and tolerability.

Exploratory endpoints will include expression levels (reported as percentage by IHC) of the fusion kinase protein. Measures taken at baseline as well as after four weeks of therapy will be summarized. Changes in expression level will be assessed between baskets using a paired t-test if data permit. For patients who progress on therapy, an additional biopsy may be obtained and will be compared with baseline expression levels if data permit. This will inform on molecular mechanisms of resistance for patients who progress while on therapy.

9.1 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.03.

10 Study Management

10.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the

Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the UCSF Institutional Review Board (IRB). Prior to obtaining

IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

10.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

10.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

10.8 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 (e.g., signed and dated consent forms and medical records, such as 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, IRB 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.

10.9 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

10.10 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

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

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Institutional Review Board (IRB). Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

UCSF will also request that all sub-sites send their Data Safety and Monitoring Plan (DSMP) to UCSF for review for approval. If a sub-site does not have its own DSMP in place, UCSF will at that time review the resources necessary to include that sub-site and determine whether the UCSF study personnel are able to manage the regulatory burden for that sub-site. Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

11 Protection of Human Subjects

11.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

11.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

12.0 References

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13.1 Appendices

Appendix 1 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 2 Multicenter Institutional Studies

Data and Safety Monitoring Plan for Multicenter Study (Phase 2 or 3 Institutional Study)

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, quarterly conference calls with the participating sites or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse Events (i.e., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol Violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites

will be faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

All grade(s) 3-5 adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the IRB must be notified.

Data and Safety Monitoring Committee Contacts

DSMC Chair:	[redacted]	DSMC Monitors
Phone:	[redacted]	Box 0128
Email:	[redacted]	UCSF Helen Diller Family
Address:	[redacted]	Comprehensive Cancer Center

[redacted] San Francisco, CA 94143

[redacted]

* DSMP approved by NCI 09/February2012

Policy/Procedure for Required Regulatory Documents for Single Site and Multicenter Investigator-Initiated Oncology Clinical Trials

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator-Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) for both IND and IND-exempt trials.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist mostly of electronic files in both iRIS and OnCore, as well as a few paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in all HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. Single Site (HDFCCC) Therapeutic Essential Regulatory Documents:

Documents Filed in iRIS:

- Current and prior versions of the Informed Consent Form(s) (ICFs).
- IRB approvals for initial submission of application, all modifications, and continuing annual renewals.
- Current and prior approved protocol versions.
- IRB roster
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event (SAE) Reports.
- Subject diary and handouts (if applicable).
- Single Patient Exception (SPE) Report(s) to IRB with Approval Letter(s) from IRB.
- Protocol Violation (PV) Reports with acknowledgement from the IRB.

Documents Filed in OnCore:

- Package Insert (if the study drug is commercial).
- Protocol signature page(s) with PI signature(s) for all protocol versions.
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC) document.
- Screening/enrollment log.
- Data and Safety Monitoring Committee (DSMC) monitoring reports.
- DSMC dose escalation approvals with study status summary forms.
- Case Report Form (CRF) completion manual.
- Drug Destruction Standard Operating Procedure (SOP).
- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature.
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, and Staff Training Documents (i.e., Collaborative Institute Training Initiative (CITI), etc.).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center.
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor.
- Drug Destruction Standard Operating Procedure (SOP).
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CV(s) and Medical License(s) of Lab Director(s), and laboratory reference ranges.

Documents Filed in Regulatory Binder:

- Delegation of Authority Log with signatures (to be scanned in OnCore once the trial is complete).

2. Additional Essential Documents for Therapeutic Multicenter Trials for the Coordinating Center (filed in OnCore or Zip Drive):

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s).
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s), will need Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for Investigational New Drug Application).
- Site Initiation Visit (SIV) minutes and correspondence with the Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s).
- Protocol Violations (PV) Reports to IRB with acknowledgement from IRB for Participating Site(s).
- Single Patient Exception (SPE) Reports to IRB with IRB Approval Letters for Participating Site(s).

- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s).
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s).
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs and Medical License(s) of Lab Director(s), and laboratory reference ranges for the Participating Site(s).
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study).
- Serious Adverse Event (SAE) forms submitted to the IRB for the Participating Site(s).

Alternate Procedures

There are no alternate procedures to the HDFCCC policy for requirements for Essential Regulatory Documents for Multicenter Investigator-Initiated Oncology Clinical Trials.

References

- ICH Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance (current version).
- International Conference on Harmonization: Good Clinical Practice: Consolidated Guideline (current version).
- International Conference on Harmonization: Essential Documents for the Conduct of a Clinical Trial (current version).
- 21CFR50
- 21 CFR56.11
- 45CFR46

21 CFR312

Required Regulatory Documents for Sub-sites Participating in Therapeutic UCSF Investigator Initiated Multicenter trial

Directions: Scan the documents in a zip drive and upload to OnCore.

1572

☐ PI and Sub investigators:

- CV and Medical license
- Financial disclosure form
- NIH or CITI human subject protection training certification

☐ Laboratories:

- CLIA &CAP and Lab Licenses
- CV and Medical License of Lab Director
- Laboratory reference ranges

Local Institutional Review Board

☐ IRB Approval letter

☐ Reviewed/Approved documents
- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

☐ Current IRB Roster

Other

☐ Delegation of Authority Log
- Include NIH or CITI human subject protection training certificates or GCP training certification

☐ Pharmacy
- Drug destruction SOP and Policy

☐ Protocol signature page

☐ Executed sub contract

Appendix 3 Prohibited Medications

The prohibited medications are basket-specific. Please refer to the drug-specific appendices for further information on prohibited medications.

- For patients with MET fusion to be treated with capmatinib, see Appendix 6, Section 6.11.
- For patients with ALK fusion to be treated with ceritinib, see Appendix 7, Section 7.11.
- For patients with RET or BRAF fusion to be treated with regorafenib, see Appendix 8, Section 8.11.
- For patients with NTRK1, NTRK2, NTRK3, or ROS1 fusion to treated with entrectinib, see Appendix 9, Section 9.11.

Each drug also has specific restrictions on the use of therapeutic and prophylactic anticoagulation. These are summarized in Table X below:

Table 4. Drug-specific restrictions on anticoagulation

Study drug	Warfarin (T)	Warfarin (P)	Heparin (T)	Heparin (P)	DTI, FXa inhibitor	Low-dose ASA	Clopidogrel
Capmatinib	With caution	With caution	Permitted	Permitted	Permitted	Permitted	Permitted
Ceritinib	Not permitted	Not permitted	Permitted	Permitted	Permitted	Permitted	Permitted
Regorafenib	Not permitted	Permitted*	Not permitted	Permitted*	Permitted	Permitted	Permitted
Entrectinib	Permitted	Permitted	Permitted	Permitted	Permitted	Permitted	Permitted

T: therapeutic
P: prophylactic
DTI: Direct thrombin inhibitor
FXa: Factor Xa
Low-dose ASA: Low-dose aspirin, <=81 mg daily

* Prophylactic doses of warfarin or heparin agents resulting in PT/INR and/or PTT <=1.5 X ULN are permitted. Infrequent bleeding or elevations in PT/INR have been reported in some subjects taking warfarin while on regorafenib therapy. Therefore, subjects taking concomitant prophylactic anticoagulation should be monitored regularly for changes in PT/INR and PTT or clinical bleeding episodes.

Appendix 4 Specimen Collection

Correlative studies assessments

Tumor biopsy specimens are to be immediately immersed in formalin.

Sample shipment instructions

For each shipment, an inventory of the samples should accompany the shipment. This inventory should include the study ID, subject ID, sample number, visit number scheduled time of collection.

The original inventory will be retained at the site in the Investigator's file.

All samples will be kept at room temperature up to and during the shipment. Unless instructed otherwise, the samples will be packed carefully with suitable packing material with absorbent material in case of leakage.

All shipments should be sent by a carrier guaranteeing overnight delivery. The following items should be considered:

- Advise the carrier of the type of service desired, need for personalized door-to-door pickup, and delivery guaranteed within 24 hours.
- Advise the carrier of the nature of the shipment's contents (human biological specimens) and label the package accordingly.

Instructions for shipment of biological samples to UCSF :

[redacted]

Instructions for shipment (and storage) of blood samples:

[redacted]