


## Using the ITR Phase I or Phase II protocol template

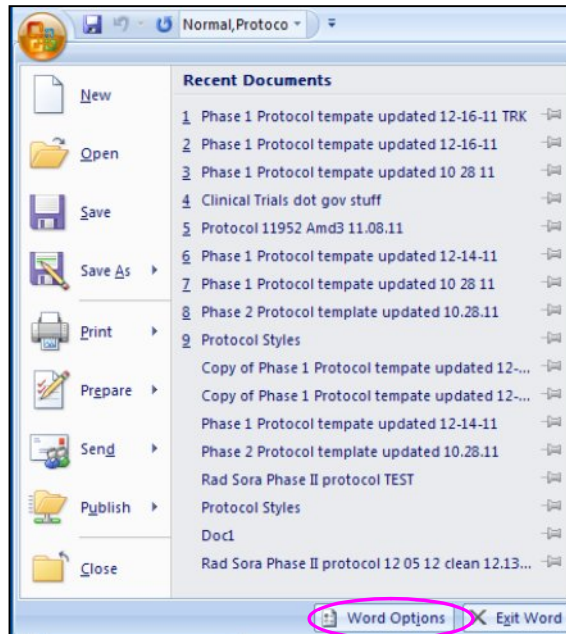
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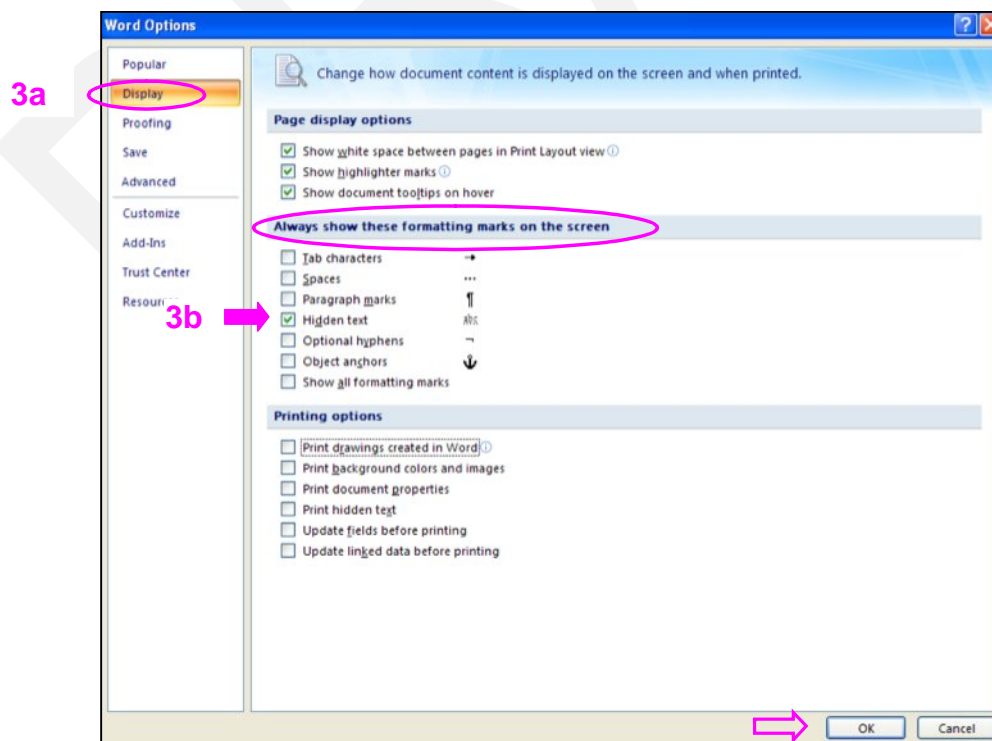
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**Protocol Number: CC #**

**Study Drug:**

**Version Number:**

**Version Date:**

**IND Number:**

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**Revision History**

Version  
Version  
Version  
Version

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## Protocol Signature Page

**Protocol No.:**

**Version Date:**

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR 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](http://www.clinicaltrials.gov) website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

### UCSF Principal Investigator / Study Chair

\_\_\_\_\_  
Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

### Participating Site(s)

Telephone:  
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Telephone:  
E-mail:

Telephone:  
E-mail:

### Principal Investigator

### Site

\_\_\_\_\_  
Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## Abstract

Title	
Patient population	
Rationale for Study	
Primary Objective	
Secondary Objectives	
Study Design	
Number of patients	
Duration of Therapy	Patients may continue treatment for << # / time frame: weeks, months, years >>from the time of study entry.
Duration of Follow up	
Duration of study	The study will reach completion << # >> weeks/months/years from the time the study opens to accrual.
Study Drugs	
Safety Assessments	
Efficacy Assessments	
Unique Aspects of this Study	

## List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CHR	Committee on Human Research (UCSF IRB)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IND	investigational new drug application

## List of Abbreviations

IP	investigational product
IRB	Institutional Review Board
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PD	disease progression
PK	pharmacokinetics
PO	<i>Per os</i> (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
QOL	Quality of Life
RBC	red blood cell (count)
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
WBC	white blood cell (count)

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## **1 Introduction**

### **1.1 Background on Indication**

### **1.2 Background on the Compounds**

### **1.3 Rationale for the Proposed Study**

### **1.4 Correlative Studies**

#### **1.4.1**

#### **1.4.2**

## **2 Objectives of the Study**

### **2.1 Primary**

- To determine the safety and tolerability of << study drug >> or combination of << study drug >> with << >>
- To determine the dose-limiting toxicity (DLT) and maximum tolerated dose for study drug when administered << schedule and list any other drugs given in combination with study drug >>
- 

### **2.2 Secondary**

- To describe the pharmacokinetics associated with << study drug >> when administered << schedule and list any other drugs given in combination with study drug >>.
- To describe any preliminary efficacy of << study drug >> or combination of << study drug >> with << >> in patients with << tumor/disease type, etc >>
- 

### **2.3 Exploratory Objectives, Other Assessments**

- 

### **2.4 Endpoints**

### 2.4.1 Primary Endpoints

### 2.4.2 Secondary Endpoints

### 2.4.3 Exploratory Endpoints

## 3 Study Design

### 3.1 Characteristics

### 3.2 Number of Subjects

### 3.3 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.

#### 3.3.1 Inclusion Criteria

1. Patients must have histologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective

OR

Patients must have histologically or cytologically confirmed << indication or study disease >>

- 2.
- 3.
4. Age >18 years
- 5.
- 6.
- 7.
- 8.
- 9.

Adequate bone marrow function:

leukocytes > 3,000/mcL  
 absolute neutrophil count > 1,500/mcL  
 platelets > 100,000/mcL"

Adequate hepatic function:

total bilirubin within normal institutional limits  
 total bilirubin within normal institutional limits  
 AST(SGOT) < 2.5 X institutional upper limit of normal  
 ALT(SGPT) < 2.5 X institutional upper limit of normal"

Adequate renal function:

creatinine within normal institutional limits  
 OR  
 creatinine clearance > 60 mL/min/1.73 m<sup>2</sup> for patients with creatinine levels above institutional normal"

10. The effects of << study drug >> on the developing human fetus are unknown. For this reason and because << drug class >> as well as other therapeutic drugs used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception: << specify which method is adequate for this study: hormonal or barrier method of birth control; abstinence, etc. >> prior to study entry and for the duration of study participation. 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 participation, and << # >> months/weeks after completion of study drug administration.
11. Ability to understand a written informed consent document, and the willingness to sign it
- 12.

### 3.3.2 Exclusion Criteria

- 1.
- 2.
- 3.
- 4.
5. Patients receiving any medications or substances that are inhibitors or inducers of CYP450 enzyme(s) are ineligible. Lists including medications and substances known or with the potential to interact with the specified CYP450 enzyme(s) isoenzymes are provided in Appendix << # >>.
6. Pregnant women are excluded from this study because << study drug >> is a/an << drug class >> drug with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with << study drug >> breastfeeding should be discontinued if the mother is treated with << study drug >>.

:“These potential risks may also apply to other drugs used in this study.”

7. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with << study drug >>. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
- 8.

### 3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for << #/time frame >> or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

### 3.5 Duration of Follow Up

Patients will be followed for 30 days after completion of treatment or removal from study, or until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.

### 3.6 Randomization Procedures

### 3.7 Study Timeline

#### 3.7.1 Primary Completion

#### 3.7.2 Study Completion

## 4 Study Drugs

### 4.1 Description, Supply and Storage of Investigational Drugs

#### 4.1.1 Investigational Drug #1

<< Drug #1 >> is available in << # >> capsules/tablets for oral administration.

### Classification

Mechanism of ActionMetabolismContraindicationsAvailabilityStorage and handling

Drug #1 is stored at << >>.

Side Effects

Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert. *[if an IB and/or package insert are available]*

**4.1.2 Investigational Drug #2**

<< Drug #2 >> is available in << # >> /mL solution in a single use-vial for intravenous administration.

ClassificationMechanism of ActionMetabolismContraindicationsAvailabilityStorage and handling

Drug #2 << >>.

Side Effects**4.2 Drug Accountability**

The Investigational Pharmacist will manage drug accountability records.

**4.3 Drug Ordering**

UCSF will obtain << study drug >> directly from pharmaceutical company as study supply.

#### 4.4 Packaging and Labeling of Study Drugs

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

### 5 Treatment Plan

#### 5.1 Dosage and Administration

Treatment will be administered on an (inpatient/outpatient) basis.

**Table 5.1 Regimen Description**

Study Drug	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Study Drug 1	Pre-medicate with << drug >> for << # >> days prior to Study Drug 1	100 mg	Oral	Days 1-3 week 1	4 weeks (28 days)
Study Drug 2	Avoid exposure to cold (food, liquids, air) for 24 hr after each dose	300 mg/m <sup>2</sup>	Intravenous	Days 1-3 week 1	
Study Drug 3	Take with food	50 mg tablet	Oral	Daily, weeks 1 and 2	

Footnotes

#### 5.1.1 Other Modality(ies) or Procedures

##### 5.1.1.1

##### 5.1.1.2

#### 5.2 Dose Escalation Schedule

**Table 5.2 Dose Escalation Schedule**

Dose Level	Dose of Study Drug*	Minimum Number of Patients
-1		3
1		3
2		3
3		3

\*Footnotes: State exact dose in units (mg/m<sup>2</sup>, µ/kg, etc.) rather than as a percentage

### 5.3 Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

Dose escalation will proceed within each cohort according to the following scheme:

**Table 5.3 Dose Escalation Schedule - DLT and MTD**

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Escalate dose to next higher dose level
1 out of 3	Enter at least 3 more patients at this dose level If 0 of these 3 additional patients experience DLT (1 of 6), proceed to the next dose level If 1 or more of the 3 additional patients suffer DLT (2 of 6), then dose escalation is stopped and this dose is declared the maximal administered dose (highest dose administered) Determination of the MTD will continue at the next lowest dose cohort, at which an additional 3 patients will be added, for a total of 6 (unless that cohort already has 6 patients)
≥ 2 out of 3	Dose escalation will be stopped This dose level is declared the maximal administered dose The next lower cohort will be expanded to 6 patients If < 1 experience DLT, this dose is the maximal tolerated dose (MTD)
≤ 1 out of 6 at highest dose level below the maximal administered dose	This is generally the recommended Phase 2 dose At least 6 patients must be entered at the recommended Phase 2 dose

Footnotes

#### 5.3.1 Dose Limiting Toxicity

Dose limiting toxicity (DLT) will be defined as << >> which are attributable to the study treatment during the first 28 days of therapy (Cycle 1). The dose limiting toxicity will be based on the tolerability observed during << Cycle # >> of treatment/observation. The maximum tolerated dose of << study drug >> will be that dose at which fewer than one-third of patients experience a dose limiting toxicity. If multiple toxicities are seen, the presence of dose limiting toxicity should be based on the most severe toxicity experienced.

The dose limiting toxicity will be defined as any grade 3 << type >> or grade 4 << type >> toxicity lasting longer than << # >> days despite << treatment/intervention >> which occurs during << Cycle # >> of treatment and observation with << study drug >> and << study drug >>, and which is attributable to the study drug(s). In addition, any grade 3 or 4 << type >> toxicity will be a dose-limiting toxicity with the exclusion of grade 3 << AE >>.

Grade 3 or 4 << AE >> will be treated with << drug >>. Grade 3 or 4 << AE >> will be treated with << drug >>.

#### 5.3.2

##### 5.3.2.1



## 5.4 Dose Modifications and Dosing Delays

**Table 5.4 Dose Modifications and Dosing Delays**

Dose Level	Dose of Study Drug
-1	
1	
2	
3	

Footnotes

Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events [Version 4.0 \(CTCAE v4.0\)](#).

### Dose Modifications and Dosing Delays Tables for Specific Adverse Events

#### Adverse Event: Nausea

Grade of Event	Management/Next Dose for << study drug >>	Management/Next Dose for << study drug >>
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1 Resume at same dose level	Hold until ≤ Grade 1 Resume at same dose level
Grade 3	Hold* until < Grade 2 Resume at one dose level lower, if indicated**	Hold* until < Grade 2 Resume at one dose level lower, if indicated**
Grade 4	Off protocol therapy	Off protocol therapy
Recommended management: antiemetics.		

\*Patients requiring a delay of > 2 weeks should go off protocol therapy

\*\*Patients requiring > two dose reductions should go off protocol therapy

**Adverse Event: Vomiting**

Grade of Event	Management/Next Dose for << study drug >>	Management/Next Dose for << study drug >>
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1 Resume at same dose level	Hold until ≤ Grade 1 Resume at same dose level
Grade 3	Hold* until < Grade 2 Resume at one dose level lower, if indicated**	Hold* until < Grade 2 Resume at one dose level lower, if indicated**
Grade 4	Off protocol therapy	Off protocol therapy
Recommended management: antiemetics.		

\*Patients requiring a delay of > 2 weeks should go off protocol therapy

\*\*Patients requiring > two dose reductions should go off protocol therapy

**Adverse Event: Diarrhea**

Grade of Event	Management/Next Dose for << study drug >>	Management/Next Dose for << study drug >>
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1 Resume at same dose level	Hold until ≤ Grade 1 Resume at same dose level
Grade 3	Hold* until < Grade 2 Resume at one dose level lower, if indicated**	Hold* until < Grade 2 Resume at one dose level lower, if indicated**
Grade 4	Off protocol therapy	Off protocol therapy
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used		

\*Patients requiring a delay of > 2 weeks should go off protocol therapy

\*\*Patients requiring > two dose reductions should go off protocol therapy

**Adverse Event: Neutropenia**

Grade of Event	Management/Next Dose for << study drug >>	Management/Next Dose for << study drug >>
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1 Resume at same dose level	Hold until ≤ Grade 1 Resume at same dose level
Grade 3	Hold* until < Grade 2 Resume at one dose level lower, if indicated**	Hold* until < Grade 2 Resume at one dose level lower, if indicated**
Grade 4	Off protocol therapy	Off protocol therapy
<< Insert any recommended management guidelines >>		

\*Patients requiring a delay of > 2 weeks should go off protocol therapy

\*\*Patients requiring > two dose reductions should go off protocol therapy

**Adverse Event: Thrombocytopenia**

Grade of Event	Management/Next Dose for << study drug >>	Management/Next Dose for << study drug >>
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1 Resume at same dose level	Hold until ≤ Grade 1 Resume at same dose level
Grade 3	Hold* until < Grade 2 Resume at one dose level lower, if indicated**	Hold* until < Grade 2 Resume at one dose level lower, if indicated**
Grade 4	Off protocol therapy	Off protocol therapy
<< Insert any recommended management guidelines >>		

\*Patients requiring a delay of > 2 weeks should go off protocol therapy

\*\*Patients requiring > two dose reductions should go off protocol therapy

**Adverse Event:**

Grade of Event	Management/Next Dose for << study drug >>	Management/Next Dose for << study drug >>
≤ Grade 1		
Grade 2		
Grade 3		
Grade 4		
<< Insert any recommended management guidelines >>		

\*Footnote any relevant guidelines regarding how long a delay in therapy is allowed before patients should go off protocol therapy

\*\*Footnote any relevant guidelines regarding how many dose reductions are allowed before patients should go off protocol therapy

**5.5 Monitoring and Toxicity Management**

Each patient receiving << study drug >> in combination with << study drug >> will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, << add other parameters >> and spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in [Section 6 Study Procedures and Observations](#). Toxicity will be assessed according to the NCI CTCAE v4.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

We will monitor for << add specific toxicity info according to this study and the study drug(s) >>.

Acute toxicity will be managed by << add specific toxicity info according to this study and the study drug(s) >>. Further management will depend upon the judgment of the clinician and may include << add specifics >>.

Patients will also be monitored for << add specifics >>. This will be monitored by << add specifics >>.

**5.5.1 Other toxicities**

**Cardiovascular toxicity** A major potential toxicity with << study drug >> is << AE >> which

will also be graded on the basis of the NCI CTCAE v4.0 scale

**Hematologic Toxicities** << State any toxicities specific to study drug(s), as applicable >>

**Viral Infection** << State any toxicities specific to study drug(s), as applicable >>

**Gastrointestinal toxicity** << State any toxicities specific to study drug(s), as applicable >>

<< insert as needed >>

<< insert as needed >>

## 6 Study Procedures and Observations

### 6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in [Section 6 Schedule of Study Procedures and Assessments](#). Screening assessments must be performed within << # >> days prior to the first dose of investigational product. Any 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  $\pm$  << # >> days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

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 Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

#### 6.1.1 Pretreatment Period

##### 6.1.1.1 Screening Assessments

The Screening procedures and assessments must be completed within << #/time frame >> of the Day 1 Visit.

- Physical examination
- Vital signs
- Complete medical history
- Baseline conditions assessment
- Documentation of disease assessment
- Performance status
- Measureable disease
- History of prior treatments and any residual toxicity relating to prior treatment
- Baseline medications taken within << # >> days of Day 1
- Sample of tumor tissue

- Hematology labs (other than CBC w/ Diff)
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
  - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH), fasting lipid panel (low-density lipoprotein [LDL], total cholesterol, triglycerides)
- Thyroid function tests: thyroid-stimulating hormone (TSH), free thyroxine (FT4)
- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Tumor marker assessments
- Immune parameter assessments
- Serum Hepatitis assessment, including Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), Hepatitis C virus RNA
- Urinalysis
- Serum or urine pregnancy test within << #/time frame >> prior to the start of study drug
- Imaging (CT or MRI) of << body locations >> for tumor/lesion assessment
- Electrocardiogram (ECG)
- Cardiac assessment
- Bone scan
- Specimen Collection for Banking
- Biopsy
- Questionnaires

## 6.1.2 Treatment Period

### 6.1.2.1 Study Procedures, Cycle 1, Day 1

- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- CBC with differential and platelet count
- Hematology labs (other than CBC w/ Diff)
- Blood chemistry assessment, including:
  - Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides)
  - Thyroid Function Tests: TSH, FT4
- Coagulation assessment, including PT/PTT/INR
- Tumor marker assessments
- Immune parameter assessments

- Urinalysis
- Serum or urine pregnancy test
- Imaging (CT or MRI) of << body locations >> for tumor/lesion assessment
- Electrocardiogram (ECG)
- Bone scan
- PK/PD/PG
- Questionnaires

#### **6.1.2.2 Study Procedures Cycle << # >>, Day << # >>**

These procedures must be completed within << #/time frame >> of Day << # >>.

- Evaluation of clinical response or deterioration
- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- Hematology assessment, including CBC with differential and platelet count
- Blood chemistry assessment, including:
  - Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel, TSH, FT4
- Coagulation assessment, including PT/PTT/INR
- Tumor marker assessments
- Immune parameter assessments
- Urinalysis
- Serum or urine pregnancy test
- Imaging (CT or MRI) of << body locations >> for tumor/lesion assessment
- Electrocardiogram (ECG)
- Cardiac Assessments (ECHO, MUGA, etc)
- Bone scan
- PK/PD/PG
- Biopsy

#### **6.1.3 End-of-Treatment Study Procedures**

To be completed within 30 days of the last dose of study drug.

- Evaluation of clinical response or deterioration
- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
- Concomitant medications

- Hematology assessment, including CBC with differential and platelet count
- Blood chemistry assessment, including:
  - Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel, TSH, FT4
- Coagulation assessment, including PT/PTT/INR
- Tumor marker assessments
- Immune parameter assessments
- Urinalysis
- Serum or urine pregnancy test
- Imaging (CT or MRI) of << body locations >> for tumor/lesion assessment
- Electrocardiogram (ECG)
- Bone scan
- PK/PD/PG
- Questionnaires

#### 6.1.4 Post-treatment/Follow Up Visits

Patients will be followed << time frame >> for up to << time frame >> after enrollment or until disease progression. The following procedures will be performed at the Follow Up Visit(s):

- Evaluation of clinical response or deterioration
- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
- Concomitant medications
- CBC with differential and platelet count
- Hematology labs (other than CBC w/ Diff)
- Blood chemistry assessment, including:
  - Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel
  - Thyroid Function Tests: TSH, FT4
- Coagulation assessment, including PT/PTT/INR
- Tumor marker assessments
- Immune parameter assessments
- Urinalysis
- Serum or urine pregnancy test
- Imaging (CT or MRI) << body locations >> (scans would only be completed in follow-up for patients whose disease has not yet progressed since entering the study)
- Electrocardiogram (ECG)
- Cardiac assessment (ECHO, MUGA, etc)
- Bone scan

### **6.1.5 Long Term/Survival Follow-up Procedures**

### **6.1.6 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 an 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.



Version date:

**Table 6.1 Schedule of Study Procedures and Assessments**

Period/ Procedure	Screening	Cycle 1					Cycle 2 and future Cycles				
Study Day/Visit Day	-# to 0 (+/- #)	1 (+/- #)	8 (+/- #)	15 (+/- #)	22 (+/- #)	29 (+/- #)	1 (+/- #)	8 (+/- #)	15 (+/- #)	22 (+/- #)	29 (+/- #)
Informed consent	X										
Baseline conditions <sup>1</sup>	X										
AE assessment		X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X
Specimen Collection or Optional Specimen Banking											
<b>Treatment/Drug Administration</b>											
<< Study drug 1 >>											
<< Study drug 2 >>											
<b>Clinical procedures</b>											
Physical exam											
Vital signs											
Medical history											
Disease assessment <sup>2</sup>											
Performance status											
Measurable disease											
Biopsy											
Questionnaire											
<< insert as needed >>											
<b>Laboratory procedures</b>											

Version date:

**Table 6.1 Schedule of Study Procedures and Assessments**

Period/ Procedure	Screening	Cycle 1					Cycle 2 and future Cycles				
Study Day/Visit Day	-# to 0 (+/- #)	1 (+/- #)	8 (+/- #)	15 (+/- #)	22 (+/- #)	29 (+/- #)	1 (+/- #)	8 (+/- #)	15 (+/- #)	22 (+/- #)	29 (+/- #)
CBC w/ Diff <sup>3</sup>											
Hematology											
Blood chemistry <sup>4</sup>											
Thyroid Function Tests											
Coagulation <sup>5</sup>											
Tumor markers <sup>6</sup>											
Immune parameters <sup>7</sup>											
Hepatitis <sup>8</sup>											
Study Labs Serum sample PK											
Urinalysis											
Pregnancy test (HCG)											
<b>Imaging procedures</b>											
Imaging (CT or MRI) <sup>9</sup>											
Cardiac Assessment (ECHO, MUGA)											
ECG/EKG											
Bone scan											

Version date:

**Table 6.1 Schedule of Study Procedures and Assessments**

Period/ Procedure	Screening	Cycle 1					Cycle 2 and future Cycles				
Study Day/Visit Day	-# to 0 (+/- #)	1 (+/- #)	8 (+/- #)	15 (+/- #)	22 (+/- #)	29 (+/- #)	1 (+/- #)	8 (+/- #)	15 (+/- #)	22 (+/- #)	29 (+/- #)

<sup>1</sup> Baseline conditions assessment per DSMC policy (Baseline Conditions VI Form)

<sup>2</sup> Disease-specific staging criteria (for CRF purposes, e.g: GU Assessment, BR Disease Eval, AML-MDS Summary, etc.)

<sup>3</sup> Including CBC with differential and platelet count

<sup>4</sup> Including alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, (BUN), creatinine, total protein, albumin, fasting glucose, potassium, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides),

<sup>5</sup> Including PT/PTT/INR

<sup>6</sup> Including CAE, AFP, CA19-9, CA 125, etc

<sup>7</sup> Immune parameter assessments

<sup>8</sup> Including HBsAg, HBsAb, HBcAb, Hep C RNA

<sup>9</sup> Restaging will occur q x <<X>> cycle

## **6.2 Usage of Concurrent/Concomitant Medications**

## **6.3 Dietary Restrictions**

## **6.4 Prohibited Medications**

## **7 Reporting and Documentation of Results**

### **7.1 Evaluation of Efficacy (or Activity)**

### **7.2**

#### **7.2.1**

#### **7.2.2 Antitumor Effect – Solid Tumors**

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 [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria (or [International Workshop on Chronic Lymphocytic Leukemia \[IWCLL\]](#)).

##### **7.2.2.1 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, 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.)

##### **7.2.2.2 Disease Parameters**

###### **Measurable disease**

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

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 total (and a maximum of two lesions per organ) 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 measurable if  $\geq 1$  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 (Tumor Markers)**

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter  $< 20$  mm with conventional techniques or  $< 10$  mm 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. (e.g. PSA, CA-125, CA19-9, CEA)

## **7.2.2.3 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**

### **Cytology, Histology**

## **7.2.2.4 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.

### **Evaluation of Non-Target Lesions**

#### Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

#### 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.

### **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 7.1 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	

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

### **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.

## **7.2.3 Antitumor Effect – Hematologic Tumors**

### **Primary Efficacy/Response assessment**

Clinical response following 3 cycles of treatment. If patient is clinically in CR (without or with cytopenias) peripheral blood should be assessed for clonal lymphocytes.

### **Final Response Assessment**

Final response assessment will occur two months following completion of treatment with study drug. It is acknowledged that to meet International Workshop on Chronic Lymphocytic Leukemia Guidelines ([iwCLL](#)) for response in CLL, a response assessment must be performed 2 months from therapy to document responses including a bone marrow to confirm CR and a CT maybe indicated or recommended. Therefore, those patients that clinically appear to be in CR will have a bone marrow biopsy and possibly a CT scan to confirm complete responses at least 3 months after all treatment.

## **7.3 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 v4.0](#) for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events, see Section << # >>.

*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.*

## **7.4 Definitions of Adverse Events**

### 7.4.1 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.

### 7.4.2 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.

#### 7.4.2.1 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.

#### 7.4.2.2 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.



### 7.4.2.3 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.

### 7.4.2.4 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.

## 7.5 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 v4.0.

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 <i>is clearly NOT related</i> to the intervention
	Unlikely	The AE <i>is doubtfully related</i> to the intervention
Related to investigational drug/intervention	Possible	The AE <i>may be related</i> to the intervention
	Probable	The AE <i>is likely related</i> to the intervention
	Definite	The AE <i>is clearly related</i> 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

## 7.6 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.

## 7.7 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<sup>®</sup>, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Committee on Human Research (CHR); 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<sup>®</sup> 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).

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore<sup>®</sup> will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis, discussed at DSMC meetings which take place every six (6) weeks, and prior to dose escalation. At the time of dose escalation, a written report will be submitted to the DSMC Chair (or qualified alternate) describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair (or qualified alternate). Approval for the dose escalation by the DSMC Chair (or qualified alternate) must be obtained prior to implementation. For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 1 Dose Escalation Institutional Study at the Helen Diller Comprehensive Cancer Center please refer Appendix 2 Data and Safety Monitoring Plan for Phase 1 Dose Escalation.

## 7.8 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 Committee on Human Research (Institutional Review Board)**

The Principal Investigator must report events meeting the UCSF CHR 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 Sponsor-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 Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 6.1.30)
- Unexpected (as defined in 0)
- Serious (as defined in 6.1.5)

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**

## **8 Statistical Considerations and Evaluation of Results**

### **8.1.1**

### **8.1.2**

#### **8.1.2.1**

## **8.2 Study Endpoints**

### **8.2.1 Study Design**

### **8.2.2 Randomization**

### **8.2.3 Stratification Factors**

## **8.3 Determination of Sample Size and Accrual Rate**

### **8.3.1 Sample Size and Power Estimate**

### **8.3.2 Replacement Policy**

### **8.3.3 Accrual estimates**

## **8.4 Interim Analyses and Stopping Rules**

## **8.5 Analyses Plans**

### **8.5.1 Analysis Population**

### **8.5.2 Primary Analysis (or Analysis of Primary Endpoints)**

### **8.5.3 Secondary Analysis (or Analysis of Secondary Endpoints)**

### **8.5.4 Other Analyses/Assessments**

## **8.6 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 v4.0.

## 8.7 Study Results

## 9 Study Management

### 9.1 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.

### 9.2 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 CHR (UCSF Institutional Review Board). Prior to obtaining CHR 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.

### 9.3 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 CHR-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.

### 9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, 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 CHR 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 CHR approval. In this circumstance, however, the Investigator must then notify the CHR 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.

## 9.5 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.

## 9.6 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.

## 9.7 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 Phase 1 Dose Escalation Institutional Study, for additional information.

## 9.8 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, biweekly conference calls with the participating sites for Phase I dose escalation studies prior to each cohort escalation and 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
- Cohort updates (i.e. DLTs)
- 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

## 9.9 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.

## 9.10 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.

## **9.11 Regulatory Documentation**

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 Committee on Human Research (CHR). Prior to implementing this protocol at the participating sites, approval for the UCSF CHR 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

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

## **10 Protection of Human Subjects**

### **10.1 Protection from Unnecessary Harm**

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR mechanism and the process of informed consent. The CHR 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 CHR 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.

### **10.2 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.

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## References

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## 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 Data and Safety Monitoring Plan\* for a Phase 1 Dose Escalation Institutional Study

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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 in each cohort
- Review of suspected adverse reactions considered “serious”
- Approval of dose escalation by DSMC Chair (or qualified alternate)
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

### Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and subject safety and discuss each subject's treatment at weekly Site Committee meetings. These discussions are documented in the Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

All institutional Phase 1 therapeutic studies are designated with a high risk assessment; therefore, the data is monitored once per month as subjects are enrolled through the DLT period.

### Adverse Event Review and Monitoring

All clinically significant 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 clinically significant adverse events entered into OnCore® will be reviewed on a weekly 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 (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 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 within **1 business day** of knowledge of the event. The contact may be by phone or e-mail.

### Dose Escalations

At the time of dose escalation, a written report will be submitted to the DSMC Chair (or qualified alternate) describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair (or qualified alternate) and written authorization to proceed or a request for more information will be issued within **2 business days** of the request. Approval for the dose escalation by the DSMC Chair (or qualified alternate) must be obtained prior to implementation.

### 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, a report should be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incidence of AEs observed in the study is within the range stated in the Investigator Brochure or package insert.

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

### Data and Safety Monitoring Committee Contacts:

DSMC Chair: Alan Venook, MD  
Phone: 415-353-2745  
Email: [venook@cc.ucsf.edu](mailto:venook@cc.ucsf.edu)  
Address: Box 1705  
UCSF  
San Francisco, CA 94115

DSMC Monitors  
Box 1297  
UCSF Helen Diller Family  
Comprehensive Cancer Center  
San Francisco, CA 94115

\* DSMP approved by NCI 09/February2012

## **Appendix 3 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)**

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### **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) where the Principal Investigator (PI) holds the IND.

### **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 of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

### **Procedures**

#### **1. HDFCCC Essential Regulatory Documents**

##### **Documents Filed in iMedRIS:**

- CHR approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Committee for Human Research (CHR) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to CHR with supporting fax documentation

##### **Documents Filed in OnCore®:**

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- DSMC dose escalation approvals with study status summary forms
- OnCore® Case Report Form (CRF) completion manual

**Documents Filed in Regulatory Binder:**

- 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, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to CHR and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

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27 April 2012

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## Appendix 4 Multicenter Institutional Studies

### 4.1 Data and Safety Monitoring Plan\* for Multicenter Institutional Study (Phase 1 Dose Escalation)

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 includes:

- Review of subject data in each cohort
- Review of suspected adverse reactions considered “serious”
- Approval of dose escalation by DSMC Chair (or qualified alternate)
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

#### Monitoring and Reporting Guidelines

All institutional Phase 1 therapeutic studies are designated with a high risk assessment. The data is monitored monthly as subjects are enrolled and includes all visits monitored up through the Dose Limiting Toxicity (DLT) period. At the time of dose escalation, a written report will be submitted to the DSMC Chair outlining the cohort dose, all adverse events and suspected adverse reactions considered “serious,” and any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the DSMC Chair or qualified alternate and written authorization to proceed or a request for more information will be issued within 2 business days of the request. The report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair’s decision, further study accrual is held while further investigation takes place.

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 weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

#### 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, 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
- Cohort updates (i.e. DLTs)
- 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

### Dose Level Considerations

The PI/Study Chair, participating investigators, and research coordinators from each site will review enrollment for each dose level cohort during the regularly scheduled conference calls. The dose level for ongoing enrollment will be confirmed for each subject scheduled to be enrolled at a site. Dose level assignments for any subject scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via fax or e-mail.

If a Dose Limiting Toxicity (DLT) arises in a subject treated at a study site, all sites must be notified immediately by the UCSF Coordinating Center. The Study Chair has 1 business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the information to all participating sites. If the DLT occurs at a participating site, the local investigator must report it to the UCSF Coordinating Center within **1 business day**, after which the UCSF Coordinating Center will notify the other participating sites.

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 sent electronically or 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.

### **Review and Oversight Requirements**

#### Adverse Event Monitoring

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

All clinically significant adverse events entered into OnCore® will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee. 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. 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" are entered into OnCore® and will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meetings, which take place every six (6) weeks.

All suspected adverse reactions considered "serious" should be reported to the UCSF Coordinating Center within **1 business day** of becoming aware of the event or during the next scheduled conference call, whichever is sooner.

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), 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 CHR must be notified.

### Data and Safety Monitoring Committee Contacts:

DSMC Chair: Alan Venook, MD  
 Phone: 415-353-2745  
 Email: [venook@cc.ucsf.edu](mailto:venook@cc.ucsf.edu)  
 Address: Box 1705  
 UCSF  
 San Francisco, CA 94115

DSMC Monitors  
 Box 1297  
 UCSF Helen Diller Family  
 Comprehensive Cancer Center  
 San Francisco, CA 94115

\* DSMP approved by NCI 09/February2012

## **4.2 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)**

### **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) where the Principal Investigator (PI) holds the IND.

### **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 of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

### **Procedures**

#### **1. HDFCCC Essential Regulatory Documents**

##### **Documents Filed in iMedRIS:**

- CHR approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Committee for Human Research (CHR) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to CHR with supporting fax documentation

##### **Documents Filed in OnCore®:**

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- DSMC dose escalation approvals with study status summary forms
- OnCore® Case Report Form (CRF) completion manual

**Documents Filed in Regulatory Binder:**

- 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, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to CHR and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

**2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)**

- 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) – 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 Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation 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 of Lab Directors, 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 both the IRB and the sponsor for the Participating Site(s)

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### 4.3 Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

- 1) Fax the documents listed below to the UCSF Coordinating center at 415-514-6995 or
- 2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

#### **1572**

☐ PI and Sub investigators:

CV and Medical license

Financial disclosure form

NIH or CITI human subject protection training certification

☐ Laboratories

CLIA and CAP

CV of Lab Director and Lab Licenses

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

Version date:

Protocol CC#:

27.apr.2012

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## Appendix 5 Prohibited Medications

<u>Drug</u>	<u>Trade name (if applicable)</u>
Aosetron:	Iotronex
Bosentan:	Tracleer
Candesartan:	Atacand
Celecoxib:	Celebrex
Diclofnac:	Volaren
Dronabinol:	Marinol
Flubiprofen:	Ansaid
Fluvastatin:	Lescol
Glimepiride:	Amaryl
Ibuprofen:	Advil, Motrin
Indomethacin:	Indocin
Irbesartan:	Avapro
Losartan:	Cozaar
Meloxicam:	Mobic
Montelukast:	Singulair
Maproxen:	Aleve
Nateglinide:	Starlix
Phenobarbital	
Phenytoin:	Dilantin
Piroxicam:	Feldene
Rosiglitazone:	Avandia
Rosuvastatin:	Crestor
Sulfmethoxazole	
Tolbutamide	
Torsemide:	Demadex
Valsartan:	Diovan
Warfarin:	Coumadin

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## Appendix 6 Specimen Collection

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### Sampling and shipping information

- Draw 2 mL into a 5 mL EDTA (K3) coated tube
- Invert the tube gently several times to avoid clotting
- Place the tube into an ice bath at approximately 4°C during the sampling period
- Within 30 min after collection, centrifuge the tube at 3-5°C for 15 min at 1500 to 2000g
- Transfer the plasma into uniquely labeled 2ML SMART SCAN TUBES from Thermo (Reference for rack/48 tubes: Nr. AB1411 or Reference for only 100 tubes: AB-1389) and frozen immediately over solid carbon dioxide (dry ice) or in a freezer at approximately -70°C or below.
- Ship frozen on dry ice to Central Lab

### 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.

Clearly indicate any missing specimens. The original inventory will be retained at the site in the Investigator's file.

All samples will be kept at the temperature specified up to and during the shipment. Unless instructed otherwise, the samples will be packed carefully with suitable packing material and dry ice to keep them frozen.

All shipments should be sent (Monday through Wednesday **only**) 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.
- Indicate Novartis drug code and Study No. on the face of the parcel to be shipped. The parcel also must carry a "dangerous goods" label because of the dry ice (labels supplied by the courier).
- The carrier must be asked to store the parcel(s) in a freezer if shipment is delayed and to replace exhausted dry ice before transportation continues.
- Shipping reservations should be made to allow delivery to Novartis before 16:00 (4 pm) local time Monday to Thursday and before 11:00 (11 am) local time on Friday. Shipments should not be sent between Thursday and Sunday, to prevent arrival over the weekend.

**Instructions for shipment of biological samples to**

All pharmacokinetic specimens will be kept at the temperature specified in the PK collection and processing section until shipment.

Samples have to be packed according to the ICAO/IATA-Packing-Instructions in an insulated box. To guarantee that the samples remain deep frozen during transport, use about **10 kg of dry ice** per box which will keep the samples frozen during the whole duration of the transport (air freight). Send the parcel to the following.

A shipping log must be included with the shipment.

Ship to:

Email:

**Please notify the addressee *in advance* of the shipment and indicate:**

- Number of the airbill
- The time and date of shipping and approximate time of arrival
- Flight Number
- To whom the shipment is addressed, the study number, carrier and the shipping form number (or equivalent airbill number)
- The sender's name, telephone number and alternative contact personnel
- The total number of cartons and unit weight of each carton

Also notify the Clinical Trial Leader at \_\_\_\_\_ when a shipment has been scheduled.

**The samples should be sent at the beginning of a week in order to arrive not later than << >>day.**

**pharmacokinetics and correlative studies assessments**

**pharmacokinetics**

Under the supervision of Drs. Yong Huang and Leslie Floren, vemurafenib analysis will be performed at UCSF.

sampling and shipping information

- Draw 2 mL into a 5 mL EDTA (K3) coated tube
- Invert the tube gently several times to avoid clotting

- Place the tube into an ice bath at approximately 4°C during the sampling period
- Within 30 min after collection, centrifuge the tube at 3-5°C for 15 min at 1500 to 2000g
- Transfer the plasma into uniquely labeled 2ML SMART SCAN TUBES from Thermo (Reference for rack/48 tubes: Nr. AB1411 or Reference for only 100 tubes: AB-1389) and frozen immediately over solid carbon dioxide (dry ice) or in a freezer at approximately -70°C or below.

Ship to:

Email:

### **Correlative studies assessments**

Portions of all new tumor biopsy specimens will be immediately immersed in formalin and subsequently embedded in paraffin and additional tissue will be flash-frozen and stored at -70 °C until the time of analysis

The primary contact for acquisition and processing of these specimens at UCSF is:

Email: