Mount Sinai *The Tisch Cancer Institute*

Clinical Trial Template Instructions:

This template has been created to assist in the development of investigator-initiated clinical trials.

The sections/language in **BLACK** are standard language for our center and should be included in your study, unless they are not applicable.

The sections/language in **BLUE** are examples and instructions and **should be modified**.

DELETE any sections that do not apply.

When the document is complete all the sections in BLUE should either be omitted or modified to the specifications of your study.

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PROTOCOL TITLE

[Include **phase** (e.g., phase I, phase II, etc.), **design** (e.g., randomized, double blind, placebo controlled, etc.), if the study **is multi-center**, the **investigational drug**, and **target disease(s) and stage** (e.g. advanced, relapsed/refractory)]

Principal Investigator:	Name Institution Address (Phone) (Fax) Email
Sub-Investigator(s):	For local sub-Is include: Name Department/Division For off-site sub-Is include: Name Institution Address (Phone) (Fax) Email
Biostatistician:	Name Institution Address (Phone) (Fax) Email
Study Drug:	Generic study drug name, followed by marketed name
IND Number:	Insert IND Number, if applicable. Delete if N/A.
IND Holder Name:	Insert name. Delete if N/A.
Funding Source:	List support (funding or investigational agent from Pharmaceutical Company(ies) or other source (provide grant number, if applicable.)
Initial version: **Amended:**	[date] (this should be the final version to be sent to the PRMC/IRB) [date]

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

TABLE OF CONTENTS

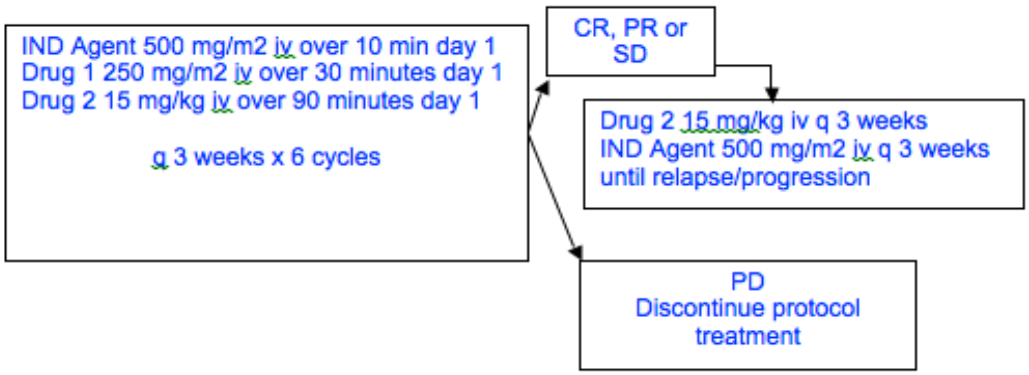
LIST OF ABBREVIATIONS

Examples Include:

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA

The schema should represent your study design, along with corresponding descriptive text, as applicable. For example:



STUDY SUMMARY

Title	Full title of protocol
Short Title	Shortened title (match this to title used in ClinicalTrials.gov)
Protocol Number	The standard protocol number used to identify this study
Phase	Clinical study phase (e.g., Phase 1, 2, 3 or 4)
Methodology	Design attributes such as single blind, double blind or open label; randomized, placebo or active placebo control; cross-over design, etc.
Study Duration	Estimated duration for the main protocol (e.g., from start of screening to last subject processed and finishing the study)
Study Center(s)	Single-center or multi-center; if multi-center, note number of projected centers to be involved
Objectives	Brief statement of primary study objectives
Number of Subjects	Number of subjects projected for the entire study (e.g., not for simply one site, rather for all sites combined)
Diagnosis and Main Inclusion Criteria	Note the main clinical disease state under study and the key inclusion criteria (i.e., not the entire list that will appear later in the protocol, rather only the key inclusion criteria)
Study Product(s), Dose, Route, Regimen	Study drug name(s) (generic name, though can also state marketed name if name-brand used in the study) and/or description of non-drug therapy (i.e., radiation, surgery, etc.); include dose, route and regimen
Duration of administration	Total duration of drug product administration (including any open-label lead-in, if applicable)
Reference therapy	Note if there is a standard reference therapy against which the study product is being compared, or if the reference is a placebo
Statistical Methodology	A very brief description of the main elements of the statistical methodology to be used in the study (as few lines as possible)

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Please provide disease background information particularly relevant to your study. Questions to be addressed may include the current standard of care and any relevant treatment issues or controversies. Please justify why an investigational therapy or approach is warranted.

1.2 Study Agent(s) Background and Associated Known Toxicities

Please provide relevant background information about the study agent(s) that you are planning to use in the study and known toxicities. The following briefly explains what is required in this section:

- A summary of findings from non-clinical in vitro/in vivo studies that have potential clinical significance including information on mechanism of action, pharmacokinetics and safety. This is particularly important for investigational agents, and may not be necessary for commercially available drugs, and/or drugs with sufficient clinical data.
- A summary from relevant clinical studies, with focus on those that provide background for your study. Please include important safety information, the rationale for the starting dose(s), information on clinical pharmacokinetics, and major route(s) of elimination. If available, please include information on the metabolism of the agent(s) in humans and address any potential for drug interactions.

1.3 Other Agents

This section may be required if your study focuses on either an investigational agent in combination with commercially available products, or if your primary objective focuses on only one of several commercial agents included in the study. If needed, please provide background information on other agent(s) and/or treatments in this study that are not described in section 1.2 including rationale for including them in this study, their mechanism of action, information to support safety issues and the rationale for the proposed starting dose scheme, if applicable. For commercially available agents, detailed information on adverse events and potential risks should be deferred until section 8.0 (Drug Information).

1.4 Rationale

Discuss reasoning behind conducting the study, and your study design. Include justification of your study endpoints. This section should link the disease background with the study agent(s) under evaluation. Include study population rationale, particularly if focusing on a subset within the disease population (e.g., relapsed or elderly patients).

1.5 Correlative Studies

If applicable, please provide the background information on the planned correlative study(ies) including the biological rationale and hypothesis.

2.0 STUDY OBJECTIVES

Please include a detailed description of Primary and Secondary objectives of the study. Each objective should receive a separate number, e.g., **2.1.1**, **2.1.2**. As an example, the following guidelines can be used to describe these objectives:

Statement of purpose: e.g., to describe, to measure, to compare, to estimate
General purpose: e.g., efficacy, safety, immunogenicity, pharmacokinetics
Specific purpose: e.g., dose-response, superiority to placebo

2.1 Primary Objectives

Note: ClinicalTrials.gov strongly encourages having only 1 primary objective and endpoint.

A typical primary objective for a phase I trial is:

2.1.1 "To determine the dose-limiting toxicity (DLT) and maximally tolerated dose for (insert Study Agent) when administered (insert schedule and list other drugs given in combination with Study Agent, if applicable)."

Each objective (whether primary, secondary or exploratory) should receive a separate number and should have a corresponding endpoint described in section 2.4.

2.2 Secondary Objectives

Typical secondary objectives for a phase I trial include:

2.2.1 "To describe the adverse events associated with (insert Study Agent) when administered (insert schedule and list other drugs given in combination with Study Agent, if applicable)"

2.2.2 "To describe the pharmacokinetics associated with (insert Study Agent) when administered (insert schedule and list other drugs given in combination with Study Agent, if applicable)"

2.2.3 "In patients with measurable disease, to describe any preliminary evidence of anti-tumor activity by assessment of objective response as determined by (insert response criteria) in patients with (insert tumor type, etc.)"

2.3 Exploratory Objectives

If applicable, please include objective(s) for your correlative studies

2.4 Endpoints

Specify which primary endpoint(s) will be used to answer your primary objective, and which secondary endpoints will be used to address your secondary objectives. Endpoints should also be described for exploratory objectives as well. A typical endpoint for the primary objective example in 2.1 would be "DLT will be defined based on the rate of drug-related grade 3-5 adverse events experienced within the first 8 weeks (2 cycles) of study treatment. These will be assessed via NCI's CTCAE v4.0 toxicity criteria. The MTD will be defined, etc."

3.0 PATIENT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

Each criterion should include its own number, e.g., 3.1.1, 3.1.2, etc.

For example:

3.1.1 Diagnosis/disease status

3.1.2 Allowable type and amount of prior therapy

3.1.3 Age ≥ 18 years.

3.1.4 Performance status

3.1.5 Adequate organ and marrow function as defined below:

- leukocytes	≥ 3,000/mcL
- absolute neutrophil count	≥ 1,500/mcL
- platelets	≥ 100,000/mcl
- total bilirubin	within normal institutional limits
- AST(SGOT)/ALT(SPGT)	≤ 2.5 X institutional upper limit of normal
- creatinine	within normal institutional limits

3.1.6 Women of child-bearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation, and for *90* days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Note: BIRTH CONTROL Language in PPHS ICF:
Recommended methods of birth control are:
The consistent use of an approved hormonal contraception (birth control pill/patches, rings), An intrauterine device (IUD), Contraceptive injection (Depo-Provera), Double barrier methods (Diaphragm with spermicidal gel or condoms with contraceptive foam), Sexual abstinence (no sexual intercourse) or Sterilization.
Some study drugs interact with hormonal contraceptives and make them less effective or they should not be used with the disease/condition under study. If that is the case, delete the hormonal methods listed above and state why they are not recommended while taking part in the study.
Men must agree to use a condom and not father a child or donate sperm for the duration of the study and for 90 days after completion of therapy

3.1.6.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.7 Other study-specific criteria

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

3.2 Exclusion Criteria

For example:

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to *Agent(s)* or other agents used in study.

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

3.2.6 Patients must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 For complicated studies (e.g., multiple treatment phases) please first provide a summary of the entire treatment plan. This should be a few sentences, which provide a "snapshot" of the treatment plan. Details will be described below.

4.1.2 Please provide a full describe of the treatment and how it will be administered (inpatient/outpatient basis). Include a description of any definite *required* or *recommended/suggested* supportive care medications.

See the example below for how the planned treatment regimen *may be presented*. Please provide separate regimen descriptions for different treatment groups of patients as necessary.

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Agent X	Premedicate with DRUG for 3 days prior to Agent X.	300 mg/m^2 in 500 cc NS	IV over 2 hours **before** Agent Y	Days 1-3, week 1	4 weeks (28 days)
Agent Y	Avoid exposure to cold (food, liquids, air) for 24 hrs after each dose.	150 mg/m^2 in 250 cc D5W	IV 1 hr after completion of Agent Y; separate IV line required	Days 1-3, week 1	
Agent Z	Take with food.	50 mg tablet	PO in the a.m.	Daily, wks 1 & 2	

For phase I dose-escalation studies: Please state the starting dose of the study agent/drug and describe the dose escalation scheme and treatment regimen. **Use exact dose rather than percentages**. Please describe the number of patients to be treated at each level and how a decision about dose escalation or

expansion of cohort sizes will be made. If there are multiple agents being used in the study, include dose escalation for each agent. Please note that escalation of only one drug at each dose level is recommended.

Please use the following table as a guideline to describe the dose escalation scheme:

Dose-Escalation Schedule		
Dose Level	**Dose of the Study Agent(s)***	**Minimum Number of Patients**
Level -1		3
Level 1		3
Level 2		3
Level 3		3
Level 4		3
*Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage		

Dose-Limiting Toxicity (DLT) and Maximally Tolerated Dose (MTD):
Please provide explicit definition of type(s), grade(s) and duration of adverse event (s) that will be considered dose-limiting, or provide definitions of other endpoints that will be used to determine dose escalations if applicable. Please note any definite exclusions from the DLT definition (e.g., if a rule states any grade 3/4 hematologic toxicity is a DLT but this EXCLUDES lymphopenia of any grade.)

Please give the specific timeframe for DLT evaluation (e.g., after 1st cycle of therapy, any time during treatment, etc.). Please also describe how you will determine the MTD, and if applicable, the recommended phase 2 dose (these will likely be one and the same). Ensure this section is consistent with the statistical section of your protocol.

Please state any special precautions or warnings relevant for agent administration (e.g., incompatibility of agent with commonly used intravenous solutions, necessity of administering agent with food, pre-medications, hydration, whether any monitoring of vital signs during or shortly after treatment is required, etc.). If treatment will be self-administered (i.e. oral drug or self-injection), please reference any subject tools that will be implemented (study medication diary, subcutaneous injection instruction sheets, etc); please also state how missed (or vomited) doses should be handled.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Insert Appropriate Section Number). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Treatment plans should explicitly identify when treatment (typically dosage) modifications are appropriate. Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear. For phase I studies, there should be consistency between toxicities which mandate dose reductions, and those events which are considered a DLT. If dose modifications or treatment delays are anticipated, please provide a dose de-escalation schema. If there are multiple agents being used in the

study, provide a detailed description of toxicity grades and method of dose modification for each agent separately. In the event that more than one study agent could be responsible for a given toxicity, please address in what order each agent should be modified/delayed and provide justification (if available). You may also want to refer reader to the appropriate section in the protocol that contains more detailed information on the potential adverse events and risks associated with each agent (either in Section 1.2,1.3 or Section 8.0). All treatment modifications should be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose. Please also address how many missed days of treatment or missed cycles warrants removal of the patient from the study. If patients may remain on study after missed days or cycles, please specify when treatment under study may resume.

You may also want to consider breaking out your dose modification schema for hematological versus non-hematological criteria. For hematological toxicity, please address guidance on use of growth factor(s). Use of a table format is recommended if applicable. The following tables are provided as examples and should be modified as appropriate:

Example 1 Hematological Toxicities

Hematological Toxicity Dose Reductions for Agent A		
ANC[1]	**Platelets**	**Action**
≥ 1,500/μL	100,000/μL	None.
1000-1499/μL	75,000-99,000/μL	*-1st Occurrence:* Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose. *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose. *-3rd Occurrence:* Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose. *-4th Occurrence*: Discontinue protocol therapy.
500-999/μL	50,000-74,000/μL	*-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose. *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose. *-3rd Occurrence*: Discontinue protocol therapy.
<500/μL	<50,000/μL	*-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Restart next treatment at TBD dose. *-2nd Occurrence*: Discontinue protocol therapy.

[1]Note: G-CSF (Filgrastim) may be added for low ANC on day of treatment *BEFORE* a dose reduction is instituted at treating physician's discretions. Neulasta® is NOT allowed.

Example 2 Non-hematological Toxicities: Modifications for several agents at once may be presented. Any exceptions should be further explained in the text of the protocol.

Non-hematological Toxicity Dose Reductions			
NCI CTC Grade	**Agent A**	**Agent B**	**Agent C**
0-2	No change from original starting dose **(Note any exceptions here and address in text)**	No change from original starting dose**(Note any exceptions here and address in text)**	No change from original starting dose **(Note any exceptions here and address in text)**
3	Hold until resolved to ≤ Grade 2, then reduce **to TBD dose**	Hold until resolved to ≤ Grade 2, then reduce **to TBD dose**	Hold until resolved to ≤ Grade 2, then reduce **to TBD dose**
Second episode of grade 3 or 4 toxicity	Hold until resolved to ≤ Grade 2, then reduce **to TBD dose**	Hold until resolved to ≤ Grade 2, then reduce **to TBD dose**	Hold until resolved to ≤ Grade 2, then reduce **to TBD dose**
Third episode of grade 3 or 4 toxicity	Remove subject from trial	Remove subject from trial	Remove subject from trial

Example 3 Non-hematological Toxicities: Each agent to be modified may have a separate table.

Example of non-hematological Toxicity Dose Reductions	
Event	**Action**
Name of Toxicity	
Grade 1-2	None
Grade 3	Insert dose modification, may want to specify if first allow attempt at control, e.g., with anti-emetics prior to dose modification
Grade 4	
Name of Separate Toxicity	
Grade 1-2	
Grade 3	

4.3 Concomitant Medications/Treatments

Please list all relevant concomitant drugs and/or treatments that are prohibited. This section should be consistent with the medications restrictions in the inclusion/exclusion criteria. If any medications may be used, but only with caution, please address that in this section.

4.4 Other Modalities or Procedures

If applicable, please provide a detailed description of any other modalities (e.g., surgery, radiotherapy) or procedures (e.g., hematopoietic stem cell transplantation) used in the protocol treatment. Please distinguish between those modalities that comprise standard of care, and those under investigation within your protocol.

4.5 Duration of Therapy

This section should unambiguously define the "end of protocol therapy." For example: "In the absence of treatment delays due to adverse events, treatment may continue for **TBD** or until:

- Disease progression

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator".

4.6 Duration of Follow Up

Include information regarding follow-up, for example, "Patients will be followed for **TBD** after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event". For Phase I studies, subjects are usually "off study" at 30 days from last treatment. Follow-up in Phase II studies will vary (e.g., 2 to 5 or even 10 years or more) depending on whether patients are followed for a survival endpoint. Please think this through carefully as following patients until death may require considerable resources, and may not be necessary. Please also state the nature and frequency of follow-up (e.g., visits every 3 months, by phone call every 6 months, etc.).

4.7 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.8 Patient Replacement

Please include guidelines describing when and how enrolled patient may be replaced in the study. For example, "Three patients within a dose level must be observed for one cycle (28 days) before accrual to the next higher dose level may begin. If a patient is withdrawn from the study prior to completing 22 days of therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level. Patients missing 7 or more doses due to toxicity will not be replaced since these patients will be considered to have experienced a dose limiting toxicity."

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within # days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history, history of infections

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status*

Performance status evaluated prior to study entry according to Appendix #/letter.

5.1.8 *Adverse event assessment*

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.1.9 *Hematology*

5.1.10 *Blood draw for correlative studies*

See Section 9.0 for details.

5.1.11 *Serum chemistries*

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.12 *Pregnancy test (for females of child bearing potential)*

See section 3.1.6.1 for definition. Distinguish between blood and urine tests for pregnancy. If pregnancy test is completed at more than one visit, it should be detailed for each visit and include which type of test is being conducted (urine or blood).

5.1.13 *Tumor assessment*

To be performed…

5.1.14 *Other*

Describe…

5.2 Procedures During Treatment

Treatment may be broken down by cycle(s) or phase(s) – whatever makes the most sense given the overall plan. Examples of treatment phases might include neoadjuvant, adjuvant, initial, maintenance, etc.

5.2.1 Prior to Each Treatment Cycle

- Physical exam, vital signs
- Hematology
- Serum chemistries

5.2.2 Day 1

- Procedure

5.2.3 30 days after treatment termination

- Physical exam, vital signs
- Hematology

- Serum chemistries

5.3 Follow-up Procedures

Patients will be followed every <time frame> after completion of (or early withdrawal from) study treatment until when.

- Procedure

5.4 Time and Events Table

Please see the example below; list the specific day or days if appropriate, e.g., Day 1, Cycle 1 or Days 1, 7… etc.). Please ensure table reconciles with study objectives, eligibility criteria, and assessments following in sections 5.1-5.3.*

SAMPLE	Pre-study	Week 1 or Day/Days	Weekly or Day/Days	q 6 Weeks	Off Treatment	Follow-up
Assessment						
Informed Consent	X					
History and PE	X			X	X	X
Performance Status	X			X	X	X
Toxicity (include DLT) Evaluations		X	X		X	
Tumor Measurements	X				X	
Chest x-ray	X	X			X	
CBC	X	X	X	X	X	
Other required labs						
Include correlative Procedures (if applicable)	X				X	

*Include any necessary notes detailing specifics of procedures outlined in table.

5.5 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Patient withdraws consent (termination of treatment and follow-up);

5.5.3 Patient is unable to comply with protocol requirements;

5.5.4 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.5.5 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the patient's best interest;

5.5.7 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.9 Lost to follow-up. *Example language: If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.*

6.0 Measurement of Effect

Use appropriate section below (solid vs. liquid tumors).

6.1 Antitumor Effect- Solid Tumors

Define/describe the criteria to be utilized (iwCLL, RANO, RECIST, other) and, if necessary, provide the justification.

If using RECIST, state:

Response and progression will be evaluated in this study 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.

6.1.1 Definitions

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

If using RECIST, state:

6.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should 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 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should 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 should 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.

Provide each method and note timeframe for when each will be done (e.g., every 6 weeks, every 2 cycles, etc.). Examples include:

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

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

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. 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 LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, 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.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

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

6.1.4.3 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.

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

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

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

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.1.5 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.

6.1.6 Progression-Free Survival

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

6.2 Antitumor Effect- Hematologic Tumors

Responses will document surrogate clinical activity and will also be reported consistent with iwCLL 2008 guidelines (see Appendix #/letter).

Baseline disease assessments will occur as indicated in Section 5.1. Final Response assessment will be assessed per iw-CLL criteria with clinical CRs confirmed by bone marrow biopsy and CT scan should be performed if previously abnormal. The primary efficacy point is response assessed following 3 cycles of treatment.

6.2.1 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.

6.2.2 Final Response Assessment- Will occur two months following completion of treatment with sorafenib. It is acknowledged that to meet iwCLL Guidelines 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 and possibly a CT scan to confirm complete responses at least 3 months after all treatment.

6.3 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events (Appendix #/letter).

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.1.1 Contraindications

7.1.2 Special Warnings and Precautions for Use

7.1.3 Interaction with other medications

7.1.4 Adverse Reactions

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.3 Definitions

7.3.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.3.2 Severity of Adverse Events

Note, some hematology studies may choose to grade toxicity using alternatives to the CTCAE v4.0 (e.g., iwCLL criteria). When an alternative is used, please modify this section as needed. If using the CTCAE state:

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

7.3.3 Serious Adverse Events

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.3.3.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.3.3.2 Is life-threatening.

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.3.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

7.3.3.4 Results in persistent or significant disability or incapacity.

7.3.3.5 Is a congenital anomaly/birth defect

7.3.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.4 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and

is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.5 Reporting Requirements for Adverse Events

7.5.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- If applicable, insert terms for expedited reporting to the pharmaceutical company/entity if they are providing funding and require expedited reporting.
- The IRB/PPHS must be notified within 5 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

  The following events meet the definition of UPR

  a. Any new information that indicates a new or increased risk, or safety issue (e.g., interim analysis, safety monitoring report, publication, updated sponsor safety report), that indicates an unexpected change to the risk/benefit ratio for the research.

  b. An investigator brochure, package insert, or device labeling is revised to indicate an increase or magnitude of a previously known risk, or describes a new risk.

  c. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in research protocol

  d. Protocol deviation or violation that harmed subjects or others or that indicated subjects or others might be at increased risk of harm.

  e. Complaint of subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm

  f. Any breach in confidentiality that may involve risk to the subject or others.

  g. Any harm experienced by a subject or other individual that in the opinion of the investigator is unexpected and at least probably related to the research procedures.

- For IND/IDE trials: The FDA should be notified within 7 business days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

7.5.2 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

7.6 Unblinding Procedures

While the safety of the subject always comes first, it is still important to seriously consider if unblinding the study therapy is necessary to ensure a subject's safety. This section should clearly describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document. For investigators, other than the sponsor-investigator, state that the investigator must inform the sponsor of all subjects whose treatment was unblinded – and describe the timelines for such reporting. In most cases, the unblinding will be part of managing an SAE, and will be reported with the SAE, however, in cases where unblinding was not associated with an SAE, such actions should be reported in a timely manner. While there is no regulation governing this timeline, it is suggested to use the same timeline requirements for investigator reporting of SAEs, (e.g., notification of sponsor within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours.)

7.7 Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, rules should be developed that clarify the circumstances and procedures for interrupting or stopping the study. If a central Data and Safety Monitoring Board (DSMB) or Committee (DSMC) is set up for the study, the stopping rules should be incorporated into their safety analysis plan as well.

If your study will have stopping rules for inadequate efficacy, describe them here.

8.0 DRUG INFORMATION

8.1 Agent XXX

For each drug provide the following:

- Other names for the drug(s):
- Classification - type of agent:
- Mode of action:
- Storage and stability:
- Protocol dose: (if a drug is given at different doses at different points in the treatment cycle, all doses should be indicated.)
- Preparation:
- Route of administration for this study:
- Incompatibilities:
- Availability: (e.g., "commercially available", "provided by sponsor"; specify if provided free of charge as this has implications for the consent form.)
- If applicable, randomization schema, blinding and placebo information

- Side effects: A brief summary of the adverse events most likely to occur in this study and associated with this agent should be inserted here. Refer the reader to the agent's package insert for a comprehensive list of adverse events.

- Nursing implications:

8.1.1 Return and Retention of Study Drug

Please include address and sponsor/Pharma/collaborator contact for the drug return and destruction policy. If remaining drug is to be destroyed, please state the drug destruction policy according to {institutional pharmacy/investigational drug services} or other appropriate instructions.

8.1.2 Please include, if applicable, plans for subject's compliance with the study agent, e.g., questionnaire, patient diary, pill diary (necessary for all oral or self-administered investigational agents), etc. Other sections may be required/requested by sponsor.

9.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to… Indicate if submission of samples for correlative studies is mandatory/optional…

9.1 Sample Collection Guidelines

What kind of samples will be collected using what. Samples will be labeled with the subject's de-identified study number and collection date and delivered for analysis to:
<Insert Location/Address>

Specify instructions for preparation and shipment (types of tubes, spun, frozen, on wet/dry ice or at room temperature, sent by overnight mail or batched, etc.) Please add any restrictions on specimen receiving times (e.g., after hours, weekends, holidays).

Samples will be collected at the following time points (+/- window):
- (Within 28 days) prior to study treatment.
- ETC…
-

9.2 Assay Methodology

9.3 Specimen Banking

<if applicable>
Patient samples collected for this study will be retained at where. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Name will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of {INSTITUTION}. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of {INSTITUTION} for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by {INSTITUTION}, the investigator or a collaborating researcher or entity. Indicate if genetic testing is a potential plan for future research.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

Here is where you describe the statistical aspects of the protocol in detail. This section should be written in coordination with the study statistician. It should precisely describe what results will be reported and how those results were calculated.

10.1 Study Design/Study Endpoints

Please specify the study design. State clearly key design aspects, such as; is the study retrospective or prospective, blinded, randomized, single or multi-centered?, etc. Define all study endpoints.

If there are stopping rules for either safety or efficacy, describe the reasoning behind them, and how they might cause a suspension of study enrollment until a safety review has been convened. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

10.2 Sample Size and Accrual

Justification for the number of patients to be used in the study must be given. Please state precisely what the statistical power and sample size considerations are for the proposed study, and which objective they address. (It should be the primary objective.) The total sample size, the total accrual, the expected accrual rate, and all relevant assumptions should be stated explicitly. How these numbers were calculated, including the software used, should be included. A reviewer should be able to duplicate the calculations given the information provided.

10.3 Data Analyses Plans

Please describe in detail how each objective (particularly the primary objective) will be addressed by a particular data analysis plan. This is where the details of each data analysis plan (for each objective) are given – stating what statistical methods will be used, and under which assumptions. Every objective, every study endpoint should have a plan associated with it. Further details concerning safety and/or pharmacokinetics, may be given here as well.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any research personnel who has a conflict of interest with this study (patent ownership, intellectual property, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must declare their conflict of interest to the appropriate institutional

review bodies. Local institutional conflict of interest policies will be followed for all research personnel associated with the research project.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Required Documentation

(For Cancer Clinical Trials Office Managed Studies multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the CCTO by all sites.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract (if applicable)

11.4 Registration Procedures

Treatment Trials utilizing biologics, drugs, or devices must register subjects through the Cancer Clinical Trials Office Subject Central Registration process. Include the following boilerplate language:

All patients must be enrolled onto trial through the Cancer Clinical Trials Office Central Registration process. Prior to registration, a member of the study staff must scan and email the following documents as individual PDF files to the Central Registration Mailbox (central.registration@mssm.edu) with a cc to the Central Registrars.

- Signed Informed Consent(s)
- Signed CCTO Registration Form
- Signed Eligibility Checklist

- Additional supporting documentation (i.e. lab/scan reports) may be included at the study teams' discretion.

The designated Central Registrar will review all received documents for consistency and completeness.

- If there is any concern or discrepancy noted, the study staff member who originated the central registration request will be contacted immediately for clarification.

If the patient is deemed eligible for study enrollment based on a thorough review by the Central Registrar, the patient will be entered into the CTMS system and a Registration Confirmation Letter is generated and sent to the following individuals:

- Study team
- Treating Physician
- Research Infusion Nurse designee
- Research Pharmacy

11.5 Data Management and Monitoring/Auditing

11.5.1 Elements of a Data and Safety Monitoring Plan

List the name(s) of the individual(s) at the Icahn School of Medicine at Mount Sinai (ISMMS) who will be responsible for data and safety monitoring of this study. For each individual, indicate their role, name, title, and department information.

ISMMS Principal Monitor:
Identify if this will be the PI, Team Member, or Independent

Last Name:
First Name:
Academic Title:
Department:
Mailing Address:
Phone:
Fax:
E-mail:

ISMMS Additional Monitor:
Identify if this will be the PI, Team Member, or Independent

Last Name:
First Name:
Academic Title:
Department:
Mailing Address:
Phone:
Fax:
E-mail:

Justify your choice of principal monitor in terms of the assessed risk to the research subject's health and wellbeing. In high risk studies when the principal monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and the rationale for selection.

List the specific items that will be monitored for safety (e.g., adverse events, subject compliance with the protocol, drop outs, etc.).

Indicate the frequency at which ACCUMULATED safety and data information (items listed in number 3 above and interim analysis of efficacy outcomes) will be reviewed by the monitor(s) or the Data Monitoring Committee (DMC). Although this information must be reviewed at least annually, the higher the study risks, the more frequently reviews must be scheduled.

Where applicable, describe rules which will guide interruption or alteration of the study design.

Where applicable, indicate dose selection procedures that will be used to minimize toxicity.

List any specialized grading system that will be used to evaluate adverse events (e.g., National Cancer Institute Common Toxicity Criteria).

Describe procedures that will be used to assure data accuracy and completeness.

Should a temporary or permanent suspension of your study occur, in addition to the PPHS, to whom (NIH, FDA, sponsor, IRB) will you report the occurrence?

11.5.2 Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB)

When appropriate, describe the DMC. Provide the number of members of the DMC, their names and area of professional expertise. DMC reports must be made available to the local PI and the TCI's DSMC. The report need not contain specifics of the study or data, but there must be assurance that subject safety is not being compromised and that the results of treatment do not warrant early termination of the study.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

11.6.2 Other Reportable New Information and Protocol Deviations/Violations

In accordance with local IRB requirements, the following information must be reported within five (5) business days.

- Non-compliance with federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance
- Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- Breach of confidentiality

- Premature suspension or termination of the research by the sponsor or investigator.

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.8 Record Retention

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

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

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12.0 REFERENCES

List all protocol references.

13.0 APPENDICES

Please list all relevant appendices in alphabetical order, e.g., Appendix A, Appendix B, etc.

Please include an appendix for a Pill Diary for all self-administered investigational agents