



**COLUMBIA UNIVERSITY  
MEDICAL CENTER**

**Herbert Irving Comprehensive Cancer Center  
Protocol**

**NCI·CC**

A Cancer Center Designated by the  
National Cancer Institute

**Columbia University Medical Center  
Herbert Irving Comprehensive Cancer Center  
Version Date:**

**CUMC IRB#:** AAA-XXXXX  
**Version Date:**

**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, investigational drug, and target disease(s)

**Coordinating Center:** Name of Institution

**Principal Investigator:** Name  
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<b>Regulatory Sponsor:</b>	Insert the Name of the Sponsor-Investigator Insert Department Name Insert Address Insert Phone Number
<b>Funding Source:</b>	Insert the Name of Primary Funding Institution Insert Address Insert Phone Number
<b>Study Agent:</b>	Insert Study Drug Name – Generic, followed by marketed name if applicable
<b>Other Agent:</b>	Insert Study Drug Name – Generic, followed by marketed name if applicable
<b>IND Status:</b>	<b>IND #:</b> Enter the # of the IND under which this study will be performed. Enter “TBD” if an IND # is not yet available. <b>IND Sponsor:</b> Enter the name of the IND holder -OR- Study Exempt from IND Requirements per 21 CFR 312.2(b)

**Affiliate Institutions:**

<b>Site Principal Investigator and Contact Information:</b>	<b>Other Investigators at Site</b>
Name of Institution <b>Principal Investigator:</b> Name Address Address Telephone Fax e-mail address	Name
Name of Institution <b>Principal Investigator:</b> Name Address Address Telephone Fax e-mail address	Name

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**Initial version:** [date]

**Amended:** [date]

**Amended:** [date]

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**Protocol Signature Page**

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

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

\_\_\_\_\_  
Signature of Principal Investigator

\_\_\_\_\_  
Date

\_\_\_\_\_  
Principal Investigator Name (Print)

\_\_\_\_\_  
Name of Institution

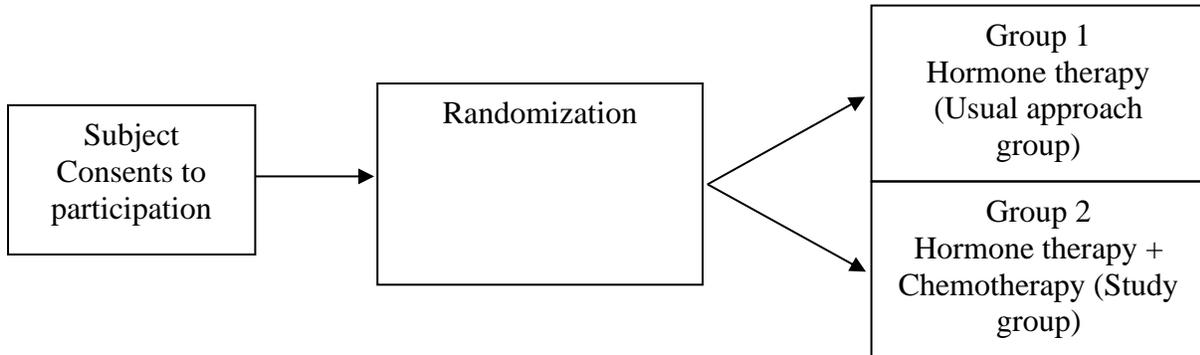
**Protocol Synopsis**

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

**Protocol Schema:**

**Insert protocol schema that shows a graphic depiction of the design of the study**

**Sample Schema:**



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## **1. INTRODUCTION**

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

## **2. STUDY OBJECTIVES**

Describe the overall objectives and purpose of the study. This should include both primary and any secondary objectives.

### **2.1 Primary Objective**

List the main objectives and endpoints in bullet point format.

### **2.2 Secondary Objective**

List the secondary objectives and endpoints in bullet point format.

## **3. BACKGROUND**

This section should contain a background discussion of the target disease state to which the investigational product(s) hold promise, any pathophysiology relevant to potential study treatment action, and its diagnosis, incidence, current treatment, and any known limitations.

## **4. INVESTIGATIONAL AGENT**

Please provide background information on the investigational product, including information to support safety issues and the rationale for the proposed starting dose, dose escalation scheme, and regimen chosen. Please also provide information on the mechanism of action, summaries of nonclinical and clinical studies, nonclinical and clinical pharmacokinetics, and major route of elimination. If available, please include information on the metabolism of the study agent in humans and its potential for drug interactions, if any. Discuss why the risks to subjects are reasonable in relation to the anticipated benefits.

### **4.1 Preclinical Data**

Summarize the available non-clinical data (published or available unpublished data) that could have clinical significance.

### **4.2 Clinical Data to Date**

Summarize the available clinical study data (published or available unpublished data) with relevance to the protocol under construction, including reference to previous evidence of the usefulness of the treatment under investigation. If none is available, include a statement affirming that there is no available clinical research data to date on the investigational product.

### **4.3 Other Agent(s)**

Please provide background information on other agent(s) and/or treatments in this study, including information to support safety issues and the rationale for the proposed starting dose and dose escalation scheme, if applicable.

## **5. STUDY DESIGN**

### 5.1 General Design

Include:

- The type/design of the study (e.g., Phase, randomized, double-blind, parallel group, etc.)
- A schematic diagram of the trial design, procedures and stages describing all arms, cohorts, or groups
- Expected duration of subject participation
- A summary description of the sequence and duration of all trial periods, including follow-up

### 5.2 Dose Limiting Toxicities

*(For Phase I or dose finding studies only):*

Include instructions detailing the timeframe for evaluating DLTs (e.g., 2 cycles or 42 days) and what would be considered a DLT including grade and duration. Also, list how many DLTs will be allowed per cohort and how the Maximum Tolerated Dose will be found.

### 5.6 Number of Patients

Total number of subjects projected for the entire study. If applicable, distinguish between the number of subjects who are expected to be pre-screened, enrolled (consent obtained), randomized, and complete the research procedures (e.g., numbers of subjects excluding screen failures) and between subgroups of subjects (e.g., healthy volunteer, disease cohort). For multicenter studies, indicate the total number of subjects to be accrued across all sites.

## **6. SUBJECT SELECTION AND WITHDRAWAL**

Each of the criteria in the following section must be met in order for a patient to be considered eligible for participation. Create a numbered list of criteria participants must be to be eligible for study enrollment at the time of registration. The following eligibility criteria must be addressed:

- Disease site/type with pathologic confirmation of diagnosis
- Extent of disease
- Allowable prior therapy and time limit since
- ECOG performance status
- Allowable laboratory values with date range
- Pathology materials submitted (of pathology review required in the study)
- Parameters listed in the study calendar which are used to determine eligibility must be identified with time frames

***The NCI protocol template inclusion/exclusion criteria are provided below for use, if applicable.***

### 6.1 Inclusion Criteria

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For phase 1 protocols: 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 there is no indicated treatment for the current clinical situation. .

OR

Patients must have histologically or cytologically confirmed Study Disease.

For phase 2 protocols: Please insert appropriate criteria for the particular patient population. Note: Lesions are either measurable or non-measurable using the criteria provided in section 13. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy. Suggested text is provided below.

Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as  $\geq 20$  mm with conventional techniques or as  $\geq 10$  mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 13.3 for more information regarding evaluation of measurable disease.

OR

Please insert appropriate criteria for diseases other than solid tumors. Criteria for selected hematologic malignancies can be found in the following references: J Clin Oncol 17(4):1244-53, 1999 (non-Hodgkin's lymphoma); J Clin Oncol 8(5):813-19, 1990 (acute myeloid leukemia); and Blood 88(12):4990-97, 1996 (chronic lymphocytic leukemia).

Please state allowable type and amount of prior therapy. Define as appropriate any limitations on prior therapy and the time from last prior regimen (e.g., no more than 6 cycles of an alkylating agent; no more than 450 mg/m<sup>2</sup> doxorubicin for agents with expected cumulative cardiotoxicity). Include separate definitions for duration as needed (e.g., at least 4 weeks since prior chemotherapy or radiation therapy, 6 weeks if the last regimen included BCNU or mitomycin C). Include site/total dose for prior radiation exposure as needed (e.g., no more than 3000 cGy to fields including substantial marrow).

Age  $\geq 18$  years. Please state reason for age restriction. If applicable, the following text can be used.

Because no dosing or adverse event data are currently available on the use of [investigational agent] [in combination with other agents] in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

ECOG performance status  $\leq 2$  (Karnofsky  $\geq 60\%$ , see Appendix A).

Life expectancy of greater than [#weeks or months].

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

- leukocytes  $\geq 3,000/\text{mcL}$
- absolute neutrophil count  $\geq 1,500/\text{mcL}$
- platelets  $\geq 100,000/\text{mcL}$
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT)  $\leq 2.5 \times$  institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance  $\geq 60 \text{ mL}/\text{min}/1.73 \text{ m}^2$  for patients with creatinine levels above institutional normal.

Please insert other appropriate eligibility criteria.

Please use or modify the following paragraph as appropriate.

The effects of [investigational agent] on the developing human fetus are unknown. For this reason and because [Agent Class] agents [as well as other therapeutic agents used in this trial] are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. 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 4 months after completion of [investigational agent] administration.

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

## 6.2 Exclusion Criteria

6.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

6.2.2 Patients who are receiving any other investigational agents concurrently.

6.2.3 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.

6.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to [investigational agent] [or other agents used in study].

6.2.5 Please state appropriate exclusion criteria relating to concomitant medications or substances that have the potential to affect the activity or pharmacokinetics of the study agent(s). Examples of such agents or substances include those that interact through the CYP450 isoenzyme system or other sources of drug interactions (e.g., P-glycoprotein). Specifically excluded substances may be listed below, stated in Section 11 (Pharmaceutical Information), and presented as an appendix. If appropriate, the following text concerning CYP450 interactions may be used or modified.

6.2.6 Patients receiving any medications or substances that are inhibitors or inducers of [specify CYP450 enzyme(s)] are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. [Appendix C is a sample patient information sheet that can be tailored to this specific protocol and presented to the patient.]

6.2.7 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.

6.2.8 The investigator(s) must state a medical or scientific reason if pregnant or nursing patients will be excluded from the study. Suggested text is provided below:

Pregnant women are excluded from this study because [investigational agent] is [a/an Agent Class] agent 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 [investigational agent], breastfeeding should be discontinued if the mother is treated with [investigational agent]. [These potential risks may also apply to other agents used in this study.]

6.2.9 The investigator(s) must state a medical or scientific reason if patients who are cancer survivors or those who are HIV positive will be excluded from the study. The full text of the Policies, Guidelines, and Procedures pertinent to this requirement is available on the CTEP Web site ([http://ctep.cancer.gov/protocolDevelopment/policies\\_hiv.htm](http://ctep.cancer.gov/protocolDevelopment/policies_hiv.htm)). Suggested text is provided below:

HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with [investigational agent]. 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.

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6.2.10 Please insert other appropriate agent-specific exclusion criteria.

6.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

*Please alter the above statement as appropriate, if necessary. In accordance with the NIH guidelines on the inclusion of women and minorities as subjects in clinical research, the Department of Health and Human Services (HHS) requires that all pilot, phase 1, phase 2, and phase 3 trials must include accrual targets for males, females, and minorities (see Section 15.2, Sample Size/Accrual Rate). The accrual targets should reflect the expected accrual over the life of the study.*

*The policy states that women and members of minority groups and their sub-populations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.*

<b>Accrual Targets</b>			
<b>Ethnic Category</b>	<b>Sex/Gender</b>		
	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	+	=	
Not Hispanic or Latino	+	=	
<b>Ethnic Category: Total of all subjects</b>	(A1) +	(B1) =	(C1)
<b>Racial Category</b>			
American Indian or Alaskan Native	+	=	
Asian	+	=	
Black or African American	+	=	
Native Hawaiian or other Pacific Islander	+	=	
White	+	=	
<b>Racial Category: Total of all subjects</b>	(A2) +	(B2) =	(C2)
(A1 = A2)		(B1 = B2)	
			(C1 = C2)

#### 6.4 Subject Recruitment

Describe how subjects will be recruited for the study (e.g., from investigator or co-investigator clinical practices, referring physicians, advertisement, etc. Note in this section any information to be disseminated to subjects (handouts, brochures, etc.) and note that any advertisements must be approved by the IRB for the site; include a sample of such information in the attachment section of the protocol, if applicable.

#### 6.5 Early Withdrawal of Subjects

##### 6.5.1 When and How to Withdraw Subjects

Describe the scenarios under which a subject may be withdrawn from the study prior the expected completion of that subject (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.) Also, if abrupt termination of study treatment could affect subject safety (e.g., in an antihypertensive study, abrupt withdrawal without other intervention might cause hypertensive rebound), describe procedure to transition subject off the study drug or to alternate therapy.

Sample language:

- If at anytime the patient develops progressive disease, he/she will be taken off study and referred for alternative therapy. .
- If at any time the patient develops unacceptable toxicity, he/she will be removed from study.
- If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (*i.e.*, a change in diagnosis), the patient will be removed from study.
- If the patient fails to comply with the defined treatment plan and follow-up evaluations, the patient will be removed from the study.
- If the patient withdraws consent for continued participation, he/she will be removed from study.

##### 6.5.2 Data Collection and Follow-up for Withdrawn Subjects

Describe the plan for collecting data from subjects that withdraw from the study. Please alter the above statement as appropriate, if necessary.

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject (though careful thought should be given to the full data set that should to be collected on such subjects to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study, attempts will be made to obtain consent from the subject to record at least survival data up to the protocol-described end of subject follow-up period. It must be a high priority to try to obtain at least survival data on all subjects lost to follow-up and to note what methods should be used before one can state the subject is

truly lost to follow-up (e.g. number of phone calls to subject, phone calls to next-of-kin if possible, certified letters, etc.). Subjects withdrawn because of unacceptable adverse events will be followed-until resolution or stabilization of the adverse event.

## **REGISTRATION PROCEDURES**

### **7.1 CUMC Research Participant Registration**

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

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

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

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

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

#### **CPDM Central Registration Procedures:**

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

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

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

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

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

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

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

**8. TREATMENT PLAN**

8.1 Agent Administration

Treatment will be administered on an [inpatient/outpatient](#) basis. Reported adverse events and potential risks for [Investigational Agent\(s\)](#) and [Other Agent\(s\)](#) are described in Section 10. Appropriate dose modifications for [Investigational Agent\(s\)](#) and [Other Agent\(s\)](#) are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Please describe the treatment regimen planned (agent, dose, route, and schedule). If appropriate, a table may be used; see an example below. Please provide separate regimen descriptions for different treatment groups of patients as necessary

Example:

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

NOTE: For orally administered agents, a method for assessing compliance with treatment should be included, e.g., “The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.”

8.1.1 Investigational Agent(s)

Please describe in detail any prophylactic or supportive care regimens required for investigational study agent(s) administration and state any special precautions or relevant

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warnings (e.g., incompatibility of agent with commonly used intravenous solutions, necessity of administering agent(s) with food, premedications, etc.).

8.1.2 Other Agent(s)

Please describe in detail any prophylactic or supportive care regimens required for administration of each other agent in the treatment, and state any special precautions or relevant warnings (e.g., incompatibility of agent with commonly used intravenous solutions, necessity of administering agent with food, premedications, etc.).

8.1.3 Other Modality(ies) or Procedures

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. If this study involves no other modalities or procedures, this section should be marked “N/A”.

8.2 General Concomitant Medication and Supportive Care Guidelines

*Please state guidelines for use of concomitant medications or any additional appropriate supportive care medications or treatments. The potential for interaction with the cytochrome P450 system should be addressed if applicable. Please use or modify the following paragraph as appropriate.*

Because there is a potential for interaction of IND Agent with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

8.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for (# cycles) or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

8.4 Duration of Follow Up

Patients will be followed for weeks after completion or removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

#### 8.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 8.5 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

### 9. DOSING DELAYS/DOSE MODIFICATIONS

*Treatment plans should explicitly identify when treatment (typically dose) modifications are appropriate. Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear. If dose modifications or treatment delays are anticipated, please provide a dose de-escalation schema.*

*The following format for an orally available agent from the NCI protocol template is provided as an example and should be modified as appropriate for this protocol:*

<b>Dose Level</b>	<b>[Agent Name] Dose</b>
-2	XX mg, schedule
-1	XX mg, schedule
0	XX mg, schedule
+1	XX mg, schedule
+2	XX mg, schedule
+3	XX mg, schedule

**Note:** *All treatment modifications must be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose.*

*For combination studies, dose modifications/treatment delays for the Investigational agent or Other Agent(s) may be presented separately or together, as appropriate. Use of a table format is recommended if applicable.*

*Below are dose modification tables for the following adverse events: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. Please use as appropriate. In addition, for your convenience, a blank dose modification table has been provided. Note in the text that if a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.*

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<u>Nausea</u>	Management/Next Dose for <i>[Agent Name]</i>	Management/Next Dose for <i>[Agent Name]</i>
≤ 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
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

<u>Vomiting</u>	Management/Next Dose for <i>[Agent Name]</i>	Management/Next Dose for <i>[Agent Name]</i>
≤ 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
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

<u>Diarrhea</u>	Management/Next Dose for <i>[Agent Name]</i>	Management/Next Dose for <i>[Agent Name]</i>
≤ 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
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go 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.		

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<u>Neutropenia</u>	Management/Next Dose for [Agent Name]	Management/Next Dose for [Agent Name]
≤ 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
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
**Patients requiring > two dose reductions should go off protocol therapy.		
<i>Insert any recommended management guidelines, if appropriate.</i>		

<u>Thrombocytopenia</u>	Management/Next Dose for [Agent Name]	Management/Next Dose for [Agent Name]
≤ 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
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
**Patients requiring > two dose reductions should go off protocol therapy.		
<i>Insert any recommended management guidelines, if appropriate.</i>		

*Example of Dose Modification Table:*

<u>Event</u>	Management/Next Dose for [Agent Name]	Management/Next Dose for [Agent Name]
≤ Grade 1	<i>Insert appropriate management guidelines in this column.</i>	<i>Insert appropriate management guidelines in this column.</i>
Grade 2		
Grade 3		
Grade 4		
*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.		
<i>Insert any recommended management guidelines, if appropriate.</i>		

## **10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS**

### 10.1 Adverse events

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

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

### 10.2 **Definitions**

#### **Adverse Event:**

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

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

#### **Serious Adverse Event:**

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

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

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

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

### **Unanticipated Problem:**

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

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

### **Adverse Event Reporting Period**

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. For this study, the study treatment follow-up is defined as xx days following the last administration of study treatment, or xx days following the decision to remove the subject from study treatment, whichever is earliest.

### **Baseline/Preexisting Condition**

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

### **General Physical Examination Findings**

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

### **Post-study Adverse Event**

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s)

that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

#### **Abnormal Laboratory Values**

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

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

#### **Hospitalization, Prolonged Hospitalization or Surgery**

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

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

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

#### **10.3 Recording of Adverse Events**

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

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

#### 10.4 Reporting of Serious Adverse Events

##### 10.4.1 IRB Notification by Sponsor-Investigator

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

##### 10.4.3 FDA Notification by Sponsor-Investigator

*When the principal investigator holds an IND, include the following:*

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The Sponsor-Investigator will also submit an IND annual report to the FDA in accordance with 21.CFR 312.33.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

#### 10.4.4 DSMC Reporting by the Sponsor Investigator

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

#### 10.4.5 Reporting to Drug Manufacturer by Sponsor-Investigator

*This section should be included, if applicable. The paragraph below should be modified based on the contract with the manufacturer.*

The Sponsor-Investigator will report to investigational agent manufacturer any serious adverse events that meet the reporting criteria to the Institutional Review Board as described in section 10.4 and/or to the FDA as described in section 10.4 within **XX hours/days** of becoming aware of it, so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

At the time of IRB renewal or at the request of the manufacturer, the Sponsor- Investigator will submit a summary of all Serious Adverse Events that have occurred inclusive of all sites to manufacturer.

### 10.5 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10.

## **11. PHARMACEUTICAL INFORMATION**

### Study Drugs

#### 11.1 Description

*This section should be a very brief synopsis of section 1.2 "Investigational agent", along with how the drug product will appear (e.g., as tablets or capsules of "X" mg, as a liquid with "X" mg dissolved in 10ml 5% dextrose and water, etc.)*

#### 11.2 Treatment Regimen

*Describe dose, route of administration, and treatment duration.*

#### 11.3 Method for Assigning Subjects to Treatment Groups

*Describe how a randomization number and associated treatment assignment will be made.*

*Note: This could be selection of a sequentially numbered drug kit/box, or communication with a randomization center that assigns a number associated with a specific treatment kit/box, etc. Alternately, the investigator can work with an independent biostatistician and the Columbia University Research Pharmacy on developing and implementing study specific randomization procedure for the project.*

#### 11.4 Preparation and Administration of Study Drug

Describe in detail all the steps necessary to properly prepare the investigational agent. Include whether the drug preparation will be done in a pharmacy or by a study team member. Fully describe how the study treatment is to be administered. If study drug is stored, mixed/prepared or dispensed from the CUMC Research Pharmacy, that should be noted here, including the contact number to that service office.

#### 11.5 Subject Compliance Monitoring

Describe how the study team will assess and track subject compliance with the study treatment regimen, and what procedures must be followed for any subject who is significantly non-compliant with the study treatment regimen.

#### 11.6 Prior and Concomitant Therapy

In this section, describe:

- What prior and/or concomitant medical therapy will be collected (if applicable).
- Which concomitant medicines/therapies (including rescue therapies) are permitted during the study
- Which concomitant medicines/therapies are not permitted during the study (if applicable)

#### 11.7 Packaging

- Describe how the investigational agent and any other agent(s) will be packaged along with the amounts (e.g., “20 ml vials containing 30 mg”, or “bottles containing 30 tablets of ...”, etc.) along with any associated labeling
- Describe if drug is to be shipped in bulk (e.g., Study drug will be shipped in boxes of 30 vials each, etc.) or as separate subject-specific kits/boxes
- When subject drug kits are constructed describe all the contents of the kit/box and associated labeling

#### 11.8 Blinding of Study Drug

Describe how the drug is blinded.

#### 11.9 Receiving, Storage, Dispensing and Return

##### 11.9.1 Receipt of Drug Supplies

Describe how drug will be obtained (e.g., what entity will ship the drug to the investigative site)

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and to what location at the site, (e.g., investigational pharmacy, etc.).

Note: Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify agent manufacturer of any damaged or unusable study treatments that were supplied to the investigator's site.

**11.9.2 Storage**

Describe storage temperature requirements, whether supplies must be protected from light, and the location of the supplies (e.g., study pharmacy). Describe any special handling requirements during storage.

**11.9.3 Dispensing of Study Drug**

Describe how the drug will be assigned to each subject and dispensed. This section should include regular drug reconciliation checks (e.g., how much drug was assigned and whether subjects actually received assigned dose or received dose properly, how much remains, how much drug was inadvertently damaged, etc. --- e.g., "Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.").

**11.9.4 Return or Destruction of Study Drug**

This section should note the procedures for final reconciliation of the site's drug supply at the end of the study, and whether study drug is to be shipped back to a source or destroyed on site. At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of the study drug.

**11.10 Other Agent(s)**

A separate pharmaceutical section is needed for each investigational agent containing at least the following information, available from the appropriate manufacturer's brochure:

**Product description:** Include the available dosage forms, ingredients, and packaging, as appropriate. Also state the agent's supplier.

**Solution preparation (how the dose is to be prepared):** Include reconstitution directions and directions for further dilution, if appropriate.

**Storage requirements:** Include the requirements for the original dosage form, reconstituted solution, and final diluted product, as applicable.

**Stability:** Include the stability of the original dosage form, reconstituted solution, and final

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diluted product, as applicable.

**Route of administration:** Include a description of the method to be used and the rate of administration, if applicable. For example, continuous intravenous infusion over 24 hours, short intravenous infusion over 30-60 minutes, intravenous bolus, etc. Describe any precautions required for safe administration.

**12. STUDY CALENDAR**

*Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate. The procedures listed in the calendar must match those included in the ICF.*

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done  $\leq 4$  weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre- Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study <sup>c</sup>
Investigational Agent		A			A			A			A			
[Other Agent(s)]		B	B		B	B		B	B		B	B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X-----X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG (as indicated)	X													
Adverse event evaluation		X-----X												X
Tumor measurements	X	Tumor measurements are repeated every <u>[# weeks]</u> weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Radiologic measurements should be performed every <u>[# weeks]</u> weeks.												X
B-HCG	X <sup>b</sup>													
Advanced imaging events, as appropriate														
Other tests, as appropriate														
Other correlative studies														

A: [CTEP and/or CIP IND Agent]: Dose as assigned; administration schedule  
B: [Other Agent(s)]: Dose as assigned; administration schedule  
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.  
b: Serum pregnancy test (women of childbearing potential).  
c: Off-study evaluation.

### **13. MEASUREMENT OF EFFECT**

*Please provide response criteria. If the criteria for solid tumors below are not applicable, the investigator(s) should provide agent- or disease-appropriate criteria (e.g., for specific hematologic malignancies, supportive care agents, etc.) with references, and all solid tumor criteria should be deleted.*

*The following format from the NCI protocol template is provided as an example and should be modified as appropriate for this protocol*

#### **13.1 Antitumor Effect – Solid Tumors**

For the purposes of this study, patients should be re-evaluated for response every [# of weeks] weeks. In addition to a baseline scan, confirmatory scans should also be obtained [# of weeks] (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

##### **13.1.1 Definitions**

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with [Agent Name].

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.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

##### **13.2 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 for non-nodal lesions and short axis for nodal lesions) as  $\geq 20$  mm by chest x-ray, as  $\geq 10$  mm with CT scan, or  $\geq 10$  mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 13.3 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 4 weeks before the beginning of the treatment.

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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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead

of CT in selected instances.

Endoscopy/Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

#### 13.4 Response Criteria

##### 13.4.1 Evaluation of Target Lesions

*Other standard disease-specific response criteria can to substituted for the suggested text.*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

##### 13.4.2 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).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: 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. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

##### 13.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until

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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.

**For Patients with Measurable Disease (e.g., Target Disease)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	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	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.  ** Only for non-randomized trials with response as primary endpoint.  *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> 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.</p>				

**For Patients with Non-Measurable Disease (e.g., Non-Target Disease)**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
<p>* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised</p>		

### 13.5 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 progressive 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, including the baseline measurements.

### 13.6 Progression-Free Survival

Include this section if time to progression or progression-free survival (PFS) is to be used. PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

### 13.7 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

#### 13.7.1 Antitumor Effect – Hematologic Tumors

Please provide appropriate criteria for evaluation of response and methods of measurement.

#### 13.7.2 Other Response Parameters

Other endpoints and the criteria for their measurement should be entered below or reference should be made to the protocol section where these criteria may be found.

### 13.8 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 and reporting it to the manufacture, if applicable. 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.

### 13.9 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.

## **14. DATA REPORTING / REGULATORY REQUIREMENTS**

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 12.2.

### 14.1 Data Collection

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

### 14.2 Data Reporting

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

### 14.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for

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safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

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

#### 14.4 Quality Control and Quality Assurance

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

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

#### Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and

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

#### 14.5 Confidentiality

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

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

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

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

#### 14.6 Source Documents

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

#### 14.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

#### 14.8 Records Retention

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

If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies);

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

### 15. STATISTICAL CONSIDERATIONS

#### 15.1 Study Design/Endpoints

Please specify the study design and primary endpoints. The design should provide for early termination for sufficiently discouraging results (e.g., by use of a 2-stage design). For the primary endpoint, indicate the “promising” range, the range of true values sufficiently promising to justify further testing of the agent (e.g., **true** response rate of at least 40%). Likewise, for the primary endpoint indicate the “discouraging” range, a range of values sufficiently discouraging to justify no further testing of the agent (e.g., **true** response rate no greater than 20%). Give the probability of a positive result, given that the true value falls within the promising range, and the probability of a negative result (along with the probability of early negative termination), given that the true value falls within the discouraging range. The ranges of promising values and discouraging values should reflect results from the single agents (or from partial combinations, if more than two agents are combined in the current regimen). These results should be referenced.

#### 15.2 Size/Accrual Rate

Please specify the planned sample size and accrual rate (e.g., patients/month).

#### 15.3 Stratification Factors

Please specify any planned patient stratification factors. Indicate whether interim monitoring and efficacy determination will be done for each stratum individually.

#### 15.4 Analysis of Secondary Endpoints

If secondary endpoints are included in this study, please specify how they will be analyzed. In particular, brief descriptions should be given of analyses of pharmacokinetic, biologic, and correlative laboratory endpoints.

#### 15.5 Reporting and Exclusions

**15.5.1 Evaluation of toxicity**

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

**15.5.2 Evaluation of response**

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

**16. PROTECTION OF HUMAN SUBJECTS**

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

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

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

and the investigator-designated research professional obtaining the consent.

## **17. STUDY FINANCES**

### **17.1 Conflict of Interest**

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

### **17.2 Subject Stipends or Payments**

Describe any subject stipend or payment here. If there is no subject stipend/payment, either delete this section or state that there are no subject payments or stipends.

## **18. PUBLICATION PLAN**

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

## **19. REFERENCES**

This is the bibliography section for any information cited in the protocol. It should be organized as any standard bibliography.

- Author, Title of work, periodical and associated information.
- Author, Title of work, periodical and associated information.

## **20. ATTACHMENTS**

This section should contain all pertinent documents associated with the management of the study. The following lists a few examples of potential attachments:

- Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)
- Sample Consent Form
- Study Procedures Flowchart/Table
- Core Lab Instructions To Investigators
- Specimen Preparation And Handling (e.g., for any specialized procedures that study team must follow to process a study specimen, and/or prepare it for shipment)
- Affiliate Site Guidelines Addendum
- Blank study tools (e.g., oral medication diaries, investigation agent reconciliation accountability forms)

