Medical College of Wisconsin

Cancer Center

Investigator-Initiated Clinical Trial Protocol Template

TEMPLATE INSTRUCTIONS

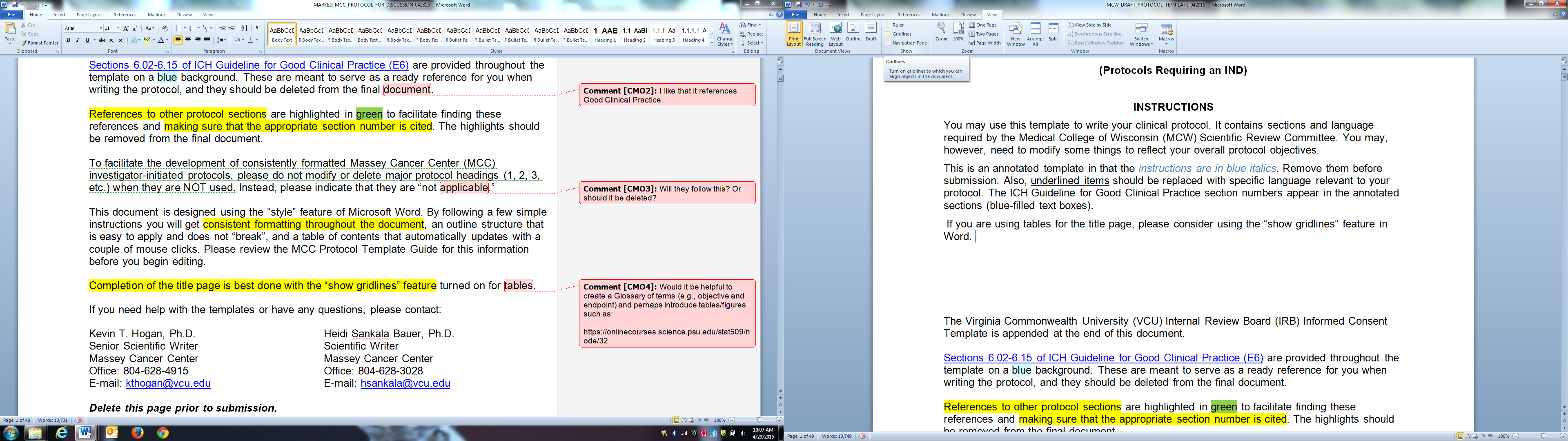
Please use this template to write your clinical protocol. It contains sections and language required by the Medical College of Wisconsin (MCW) Scientific Review Committee and the Institutional Review Board. You may, however, need to modify some sections to reflect your overall protocol objectives. Also, please delete sections that are not relevant to your study (rather than writing “not applicable”).

This is an annotated template in that the instructions are in blue italics. Remove them before submission. Also, underlined items should be replaced with specific language relevant to your protocol.

The ICH Guideline for Good Clinical Practice section numbers appear in the annotated sections (blue-filled text boxes). Remove boxes prior to submission.

References to other protocol sections are highlighted in green to facilitate finding these references and making sure that the appropriate section is cited. These highlights should be removed from the final document.

If you are using tables for the title page (page nos. 3 and 4), please consider using the “show gridlines” feature in Word.



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**TEMPLATE VERSION HISTORY**

| **Version** | **Date** | **Date** |
| --- | --- | --- |
| v2021-02 | 2/11/21 | * Updated language and tables in *Adverse Events: Definitions, Collection, and Reporting Requirements* section. |
| v2021-08 | 8/26/21 | * Fixed outdated MCW DSMP link in *Data and Safety Monitoring Plan* section. |
| v2021-09 | 09/22/21 | * Began tracking changes made to the MCW IIT Protocol Template * Added following language clarifying the reporting and consequence of protocol deviations to the *Regulatory Compliance, Ethics, and Study Management* section, *Changes in the Protocol* subsection. |
| v2021-11 | 11/03/21 | * Added standard language to *Publishing Data* subsection:   All raw data, data figures, data interpretation, models, and conclusions drawn from this study will be managed by the principal investigator and co-investigators listed in this protocol. The findings from this study are to be presented at relevant conferences/meetings followed by a plan to publish in a respectable peer-reviewed journal. The principal investigators, with assistance from study team members, will be responsible for drafting, overseeing, and finalizing conference abstract submissions, poster and/or oral presentations, or manuscript submission(s) to the journal.  For any manuscript that is to be published in a journal, the role of authors/contributors, the disclosure of financial/non-financial relationships and activities, and the report of perceived conflicts of interest will largely adhere to the recommended guidelines set forth by the International Committee of Medical Journal Editors (ICMJE; [Defining the Role of Authors and Contributors](http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), [Disclosure of Financial and Non-Financial Relationship and Activities and Conflicts of Interest](http://www.icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html)). The PI(s) will coordinate to determine who will be listed as first, senior, and corresponding author(s). Study team members who have made substantial and significant intellectual contributions to the study and its findings will be listed as contributing authors or, in certain circumstances, acknowledged. Funding sources and any conflict of interests, perceived or actual, will be disclosed and stated within the appropriate section of the manuscript at submission. |
| v2021-11.1 | 11/12/21 | * Introduced specific time frame (i.e., ≥24 hours) of inpatient hospitalization in the *Serious Adverse Event (SAE)* subsection:   Requires inpatient hospitalization ≥24 hours or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).   * Added the following in the Drug Manufacturer SAE *Reporting Instructions* subsection to avoid deviations associated with SAEs that must be reported to the sponsor/drug manufacturer within 24 hours after study staff awareness, which now reads as follows:   *At MCW Cancer Center CTO’s request, please include the following language if working with a specific company/grantor:*  In addition to institutional and federal guidelines and per drug manufacturer requirements, all SAEs that occur after the subject has signed the consent form through 30 days post last dose of study drug(s) will be reported within 24 hours of study staff awareness (or in the case of a weekend or holiday, next business day), using OnCore®, which is to be entered in the SAE tab. |

***Delete this page prior to submission.***

* This is the cover page. Please note that the version number is on the cover page and also in the bottom footer.

****

CLINICAL STUDY PROTOCOL

Short Protocol Title

Long Protocol Title

Clinical Trials.gov Number (If available)

Investigator(s) Name, Credential

Current Version Number and Date

Proprietary and Confidential

The information in this document is considered privileged and confidential, and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board approval and informed consent, or as required by federal and state laws. Persons to whom this information is disclosed should be informed that this information is privileged and confidential and that it should not be further disclosed.

|  |  |
| --- | --- |
| Title: *Insert title here*. | |
| MCW OnCore® No.: *Assigned initially.*  MCW Protocol No.: *IRB will assign.* | FDA IND No.: *FDA will assign.* |
| **Principal Investigator/Study Chair/Coordinating Center/Sponsor-Investigator:** (Use one as appropriate)  *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax*  *Email address* | **IND Sponsor:** (If not sponsor-investigator)  *Name*  *Address*  *Address*  *Telephone*  *Fax*  *Email address* |
| **Sub-investigator/Responsible Investigator:** (Use one as appropriate)  *A responsible investigator must be listed for each participating site in a multi-institutional study*  *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax*  *Email address* | **Sub-investigator/Responsible Investigator:** (Use one as appropriate)  *Same information as per PI*  *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax*  *Email address* |
| **Sub-investigator/Responsible Investigator:** (Use one as appropriate) *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax Email address* | **Sub-investigator/Responsible Investigator:** (Use one as appropriate) *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax*  *Email address* |
| **Sub-investigator/Responsible Investigator:** (Use one as appropriate)  *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax*  *Email address* | **Sub-investigator/Responsible Investigator:** (Use one as appropriate)  *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax*  *Email address* |
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| **Laboratory Contact:**  *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax*  *Email address* | OnCore®**Contact:**  *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax*  *Email address* |
| **Funding Sponsor:** (or other designation as appropriate; delete if not needed)  *Name Contact information* | **Pharmacist:**  *Name*  *Title*  *Institution*  *Address*  *Telephone*  *Fax* |
| Investigational Agent(s): *List each agent name and indicate if its use is “commercial” or “investigational use” stock. Do not describe the agents. This information is also in the protocol summary and described at length throughout the protocol.* |  |

**Version History**

**Version 1, Version Date MM/DD/YYYY**

Initial submission of the protocol.

|  |  |
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| **Version** | **Date** |
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# Protocol Summary

*This is meant to be brief. Limit the protocol summary to* ***no more than two pages****. Make sure that the items listed on this page match with the items in the rest of the document.*

*Black sections are required, while blue can be kept or removed per your preference.*

|  |  |
| --- | --- |
| **Title** |  |
| **IND Sponsor** | *If applicable* |
| **Principal Investigator** |  |
| **Clinical Trial Phase** | *I, II, III or IV* |
| **Study Population** | *[As described in Section 1, e.g., specific mutation, treatment history, etc.]* |
| **Primary Objectives** | *[Matches the objective(s) described in Section 2 Objectives of the Study — there should only be one primary objective.]* |
| **Secondary Objectives** | *[Matches the objective(s) described in Section 2.]* |
| **Endpoints** | *[Matches those described in Section 2.]* |
| **Study Design** | *[Brief summary of Section 11 Study Design; Describe the trial type/design (e.g., double-blind, placebo-controlled, parallel design)]* |
| **Study Agent/‌Intervention Description** | *[Names, dosage, and brief description of information in Sections 5 and 8.]* |
| **Number of Subjects** | *[As described in Sections 3 and 11.]* |
| **Subject Participation Duration** | Patients may continue treatment for << # / time frame: weeks, months, years >> from the time of study entry. Patient follow-up continues for << # / time frame: weeks, months, years >>.  *[Duration of therapy for individual patients, not duration of the study.]* |
| **Estimated Time to Complete Enrollment:** |  |

Schema

*Insert a schema (figure or table) that concisely describes the study. A schema should be used for complex studies (more than one arm), but a simple phase I study may not require a schema.*

*We suggest using one of the following programs:*

[**Draw.io**](https://www.draw.io/) -- Online diagram software for making flow charts, process diagrams, org charts, UML, ER and network diagrams.

[**Microsoft Visio**](https://products.office.com/en-us/visio/flowchart-software) – A user-friendly diagramming and vector graphics application that is part of the Microsoft Office family.

[**Lucidchart**](https://www.lucidchart.com/pages/signup?utm_expid=39895073-174.FtMvh7TORVKb0Kp82Fb6Hw.1&utm_referrer=https%3A%2F%2Fwww.google.com)– A nice site for creating a variety of different charts and diagrams. Also, it is a very easy site to use with a drag-n-drop interface.

[**Diagramly**](http://www.diagram.ly/) – A site for creating diagrams, flow charts, and more that is similar to Lucid Chart.

[**Lovely Charts**](http://www.lovelycharts.com/) - An easy site to use to make polished charts.

# Study Calendar

* The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered a source of data. [GCP 6.4.9]
* Methods and timing for assessing, recording and analyzing efficacy parameters. [GCP 6.7.2] (See also Section 9 MEASUREMENT OF EFFECT; Section 11 STATISTICAL CONSIDERATIONS.)
* The methods and timing for assessing, recording, and analyzing safety parameters. [6.8.2] (See also Section 5 TREATMENT PLAN; Section 7 ADVERSE EVENTS; Section 11 STATISTICAL CONSIDERATIONS; Section 12 DATA AND SAFETY MONITORING PLAN.)

The below study chart is described in detail in Section 5 Treatment Plan.

*The Study Calendar is a chart. These calendars should outline every parameter/test, which will be performed while the patient is on the study, along with the actual therapy. Write it so that it can be copied for each patient and used by the nurse/data manager/physician for patient management.*

*Every test, whether it is being done prestudy only or continuously throughout the study, should be noted.*

*Include windows for timing of treatments/assessments (e.g., 6 weeks +/- 5 days), as this will reduce the number of study deviations.*

*It is not necessary to list every day or week throughout the study’s life; rather, only those days in which either therapy or tests are being performed. Asterisk and footnote special instructions. All tests that will be continued after the patient stops therapy should also be indicated along with the time point at which they should be performed.*

*Please note that the below tables are simply suggestions.*

| SAMPLE Study Calendar Example  This table works as required for OnCore® calendar/CRF/billing configuration.  List assessments and procedures in the same order as listed in previous section text and list similar types of procedures together (e.g., labs, imaging, exams). Use/modify schedule table as needed.  +/- #: if the window is the same # of days for each cycle and visit, one footnote may be added to describe and text in each column may be deleted. | | | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Period/**  **Procedure** | **Screening** | **Cycle 1** | | | | | **Cycle 2 and future Cycles** | | | | | **End of Treatment visit** | **Follow-up visits** |
| **Study Day/Visit Day** | **-# to 0 (+/- #)** | **1 (+/- #)** | **8 (+/- #)** | **15 (+/- #)** | **22 (+/- #)** | | **1 (+/- #)** | **8 (+/- #)** | **15 (+/- #)** | **22 (+/- #)** | | **# (+/- #)** | **FU # (+/- #)** |
| Informed consent | X |  |  |  |  | |  |  |  |  | |  |  |
| Baseline conditions 1 | X |  |  |  |  | |  |  |  |  | |  |  |
| AE assessment |  | X | X | X | X | | X | X | X | X | | X | X |
| Concomitant medications |  | X | X | X | X | | X | X | X | X | | X | X |
| Specimen collection or optional specimen banking |  |  |  |  |  | |  |  |  |  | |  |  |
| **Treatment/Drug Administration** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| << Study drug 1 >> |  |  |  |  |  | |  |  |  |  | |  |  |
| << Study drug 2 >> |  |  |  |  |  | |  |  |  |  | |  |  |
| **Clinical procedures** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Physical exam |  |  |  |  |  | |  |  |  |  | |  |  |
| Vital signs |  |  |  |  |  | |  |  |  |  | |  |  |
| Medical history |  |  |  |  |  | |  |  |  |  | |  |  |
| Disease assessment 2 |  |  |  |  |  | |  |  |  |  | |  |  |
| Performance status |  |  |  |  |  | |  |  |  |  | |  |  |
| Measurable disease |  |  |  |  |  | |  |  |  |  | |  |  |
| Biopsy |  |  |  |  |  | |  |  |  |  | |  |  |
| Questionnaire |  |  |  |  |  | |  |  |  |  | |  |  |
| *<< insert as needed >>* |  |  |  |  |  | |  |  |  |  | |  |  |
| **Laboratory procedures** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CBC w/ diff 3 |  |  |  |  |  | |  |  |  |  | |  |  |
| Hematology |  |  |  |  |  | |  |  |  |  | |  |  |
| Blood chemistry 4 |  |  |  |  |  | |  |  |  |  | |  |  |
| Thyroid function tests |  |  |  |  |  | |  |  |  |  | |  |  |
| Coagulation 5 |  |  |  |  |  | |  |  |  |  | |  |  |
| Tumor markers 6 |  |  |  |  |  | |  |  |  |  | |  |  |
| Immune parameters 7 |  |  |  |  |  | |  |  |  |  | |  |  |
| Hepatitis 8 |  |  |  |  |  | |  |  |  |  | |  |  |
| Study labs  serum sample PK |  |  |  |  |  | |  |  |  |  | |  |  |
| Urinalysis |  |  |  |  |  | |  |  |  |  | |  |  |
| Pregnancy test (HCG) |  |  |  |  |  | |  |  |  |  | |  |  |
| **Imaging procedures** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Imaging (CT or MRI) 9 |  |  |  |  |  | |  |  |  |  | |  |  |
| Cardiac assessment (ECHO, MUGA) |  |  |  |  |  | |  |  |  |  | |  |  |
| ECG/EKG |  |  |  |  |  | |  |  |  |  | |  |  |
| Bone scan |  |  |  |  |  | |  |  |  |  | |  |  |
| 1. Baseline conditions assessment per DSMC policy. 2. Disease-specific staging criteria (for CRF purposes, e.g., GU Assessment, BR Disease Eval, AML-MDS Summary, etc.). 3. Including CBC with differential and platelet count. 4. Including alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides). 5. Including PT/PTT/INR. 6. Including CAE, AFP, CA19-9, CA 125, etc . 7. Immune parameter assessments. 8. Including HBsAg, HBsAb, HBcAb, Hep C RNA. 9. Restaging will occur q x <<X>> cycle.   *[Please provide a window for assessments when applicable.]* | | | | | | | | | | | | | |

# List of Abbreviations

|  |  |
| --- | --- |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical (Classification System) |
| AUC | area under the curve |
| BUN | blood urea nitrogen |
| CBC | complete blood cell (count) |
| CR | complete response |
| CRC | clinical research coordinator |
| CRF | case report form |
| CSF | cerebral spinal fluid |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| CTMS | Clinical Trial Management System |
| DFS | disease-free survival |
| DLT | dose-limiting toxicity |
| DSMC | Data and Safety Monitoring Committee |
| DSMP | data and safety monitoring plan |
| ECOG | Eastern Cooperative Oncology Group |
| FCBP | female of childbearing potential |
| FDA | Food and Drug Administration |
| GCP | good clinical practice |
| HBeAg | hepatitis B “e” antigen |
| HBV | hepatitis B virus |
| HCT | hematocrit |
| HCV | hepatitis C virus |
| HGB | hemoglobin |
| HIV | human immunodeficiency virus |
| ICH | International Conference on Harmonization |
| IND | investigational new drug application |
| IP | investigational product |
| IRB | Institutional Review Board |
| iwCLL | International Workshop on Chronic Lymphocytic Leukemia |
| IV | intravenous |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| MCWCC | Medical College of Wisconsin Cancer Center |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| NHL | non-Hodgkin lymphoma |
| ORR | overall response rate |
| PD | disease progression |
| PK | pharmacokinetics |
| PO | per os (by mouth, orally) |
| PR | partial response |
| QOL | quality of life |
| RBC | red blood cell (count) |
| SAE | serious adverse event |
| SD | stable disease |
| SD | standard deviation |
| SRC | Scientific Review Committee |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| ULN | upper limit of normal |
| UP | unanticipated problem |
| UPIRSO | unanticipated problems involving risks to subjects or others |
| WBC | white blood cell (count) |

# Background

PURPOSE: This section provides a brief but comprehensive introduction that should summarize others’ findings and address knowledge gaps. It provides a compelling argument that justifies the proposed research.

* Name and description of the investigational product(s). [GCP 6.2.1]
* Prior Literature and Studies: A findings summary from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to your trial. [GCP 6.2.2]
* Summary of known and potential risks and benefits, if any, to human subjects. [GCP 6.2.3]
* Description of and justification for the route of administration, dosage, dosage regimen and treatment period(s). [GCP 6.2.4]
* Description of the population to be studied. [GCP 6.2.6]
* References to literature and data that are relevant to the trial, and that provide background for the trial. [GCP 6.2.7]

*The outline below illustrates one way in which the background information can be organized in this section. However this information is organized, it is important to include each of the items required by Good Clinical Practice (GCP) guidance.*

## Study Disease (replace header with study disease)

*Provide background information related to the disease to be studied.*

*Provide background rationale for evaluating this intervention in this disease. Survey current treatment options for patient population and review clinical outcomes for these treatments. Discuss reasons for conducting this study and briefly summarize study design; this is described in detail in Section 11 of this document. This section should connect the disease background with the study drugs under evaluation and provide a brief overview of the study. Indicate why this information is valuable and how it advances knowledge. Identify possible risks and benefits; how risks will be mitigated in the study, and why potential benefits outweigh the risks.*

**Investigational Agent(s)**

*This is intended to be a brief summary of Section 8 Pharmaceutical Information — provide summary information on each investigational study drug, device or procedure, including the mechanism of action, summaries of nonclinical and clinical studies, nonclinical and clinical pharmacokinetics, major elimination route, safety profile and the rationale for the starting dose, dose escalation scheme, and regimen chosen. Include any information on the metabolism of the investigational study drug in humans and its potential for drug interactions, (e.g., via the P450 enzyme system).*

*Replace header with investigational agent; use additional headers if more than one investigational agent is used.*

*The “Preclinical Data” and “Clinical Data” sections below may be useful in organizing this information. They may be used or deleted as appropriate.*

### **Preclinical Data**

### **Clinical Data**

### **Known Risks and Potential Benefits**

### **Rationale**

## Other Agents (replace header with other agents used in the study)

## Correlative Studies Background

*Provide background information on each planned correlative study, including the biological rationale and hypothesis, as well as the relevant preclinical and clinical data (if available). For additional information, see FDA’s Guidance* [*Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories*](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073162.pdf) *and CTEP’s* [*Guidelines for Correlative Studies in Clinical Trials*](http://ctep.cancer.gov/protocolDevelopment/templates_applications.htm). *If this trial includes no correlative studies, state “No correlative studies will be conducted in this study.”*

# Hypothesis, Objectives, and Endpoints

PURPOSE: The hypothesis addresses the primary question by providing a tentative answer. The precise objective states the questions (to describe, measure, evaluate). Endpoints drive the study design. They address practical, real and significant needs (e.g., improve symptoms, survival, etc.).

* A detailed description of the hypothesis, objectives and the trial purpose. [GCP 6.3]
* A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial. [6.4.1]

*Provide detailed description of primary and secondary objectives, and describe any other assessments that will be performed in this study. The objectives should state the scientific question(s) that the study seeks to answer. The objectives — ‘to describe,’ ‘to measure,’ to compare,’ ‘to estimate’ — may be stated in general terms: efficacy, safety, immunogenicity, pharmacokinetics; or specific: dose-response, superiority to placebo. Include the name(s) of the study drug(s) or intervention being evaluated, doses or dose ranges to be studied, dose regimens, etc. The objectives should indicate why the study is being done and differ from the study endpoints, which are the parameters used to evaluate the objectives. The study endpoints are in the Study Design. The primary objectives are generally therapeutic in nature (to assess the safety of…, to determine the efficacy of…, to determine the DLT [dose-limiting toxicity] of…) while the secondary objectives are frequently related to correlative studies.*

## Primary Objectives

State the primary protocol objective. It should have a corresponding endpoint described in Sections 3 and 11. For example, a typical primary objective for a phase 1 trial is:

### To determine the safety and tolerability of << study drug >> or combination of << study drug >> with << >>.

* + 1. To determine the dose-limiting toxicity (DLT) and maximum-tolerated dose for study drug when administered << schedule and list any other drugs given in combination with study drug >>.

## Secondary Objectives

Insert secondary objectives, if any, here. Typical secondary objectives for a phase 1 trial may be:

### To describe the pharmacokinetics associated with << study drug >> when administered << schedule and list any other drugs given in combination with study drug >>.

### To describe any preliminary efficacy of << study drug >> or combination of << study drug >> with << >> in patients with << tumor/disease type, etc. >>.

## Rationale for the Outcome Measures Selection

## Primary Endpoint(s)

*The primary endpoints are the clinical, chemical, biological, etc. parameters that are being measured to evaluate the primary objective(s). The clinical trial* ***primary endpoint*** *is the endpoint for which subjects are randomized and for which the trial is powered. This information should be identical to Section 11. A typical endpoint for the primary objective example above would be:*

### *DLT will be defined, based on the rate of drug-related grade 3–5 adverse events. These will be assessed using the NCI CTCAE v5.0. The MTD will be defined, etc.*

## Secondary Endpoint(s)

*The secondary endpoints, if any, are the clinical, chemical, biological, etc. parameters that are being measured to evaluate the secondary objective(s). “****Secondary endpoints*** *are endpoints that are analyzed post hoc, for which the trial may not be powered nor randomized.”*

## Exploratory Endpoints

*A trial might also define exploratory endpoints that are less likely to be met.*

Example Summary Table

| **OBJECTIVES** | **ENDPOINTS** | **JUSTIFICATION FOR ENDPOINTS** |
| --- | --- | --- |
| **Primary** |  |  |
| The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing). | The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective (e.g., “the study wins”). Often phase 2 and 3 trials include primary objectives, and therefore primary endpoints, to demonstrate effectiveness. Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold. However, this is not always the case. For example, in many trials of medical devices there are primary endpoints for both safety and effectiveness.  In a trial designed to establish efficacy, a primary endpoint should measure a clinically meaningful therapeutic effect or should have demonstrated ability to predict clinical benefit. | Briefly explain why the endpoint(s) were chosen. |
| **Secondary** |  |  |
| The secondary objective(s) are goals that will provide further information on the use of the intervention. | Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. Secondary endpoints are those that may provide supportive information about the study intervention’s effect on the primary endpoint or demonstrate additional effects on the disease or condition. It is recommended that the list of secondary endpoints be short, because the chance of demonstrating an effect on any secondary endpoint after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases. | Briefly explain why the endpoint(s) were chosen. |
| **Tertiary/Exploratory** |  |  |
| Tertiary/exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research. | Exploratory endpoints should be specified. Exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses.  Endpoints that are not listed in an alpha conserving plan will be considered exploratory. | Briefly explain why the endpoint(s) were chosen. |

# Study Design

PURPOSE: The study design presents how and when these will be measured. This section provide a brief overview.

* A description of the type/design of the trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages. [6.4.2] (See also the SCHEMA Section.)
* A description of the measures taken to minimize/avoid bias, including: (a) randomization; (b) blinding. [6.4.3]

*When writing this section, please make sure that you have met with the OnCore® representative and your biostatistician.*

## General Description

*State a short description of the study, including phase, type (treatment, prevention, diagnostic, etc.), interventional model (single group, parallel, cross-over, etc.), number of intervention arms, if the study is open label, single or double blinded, and whether the study is randomized. State the primary outcome that the protocol is designed to evaluate: safety, efficacy, pharmacokinetics, pharmacodynamics.*

## Primary Completion

*Estimate the length of time it will take for the study to reach primary completion from the time the study opens to accrual to the date that the final subject is expected to be examined or receive an intervention for the purposes of final data collection for the primary outcome. For example:*

*The study will reach primary completion 24 months from the time the study opens to accrual.*

## Study Completion

*Estimate the length of time it will take for the study to reach study completion from the time the study opens to accrual to the final date on which data are expected to be collected. For example:*

*The study will reach study completion 36 months from the time the study opens to accrual.*

# Subject Participation, DIscontinuation, and Withdrawal

MCW must follow all MCW IRB requirements and policies regarding subject participation, found here:

<https://www.mcw.edu/HRPP/Policies-Procedures.htm>

## Subject Status

Subject statuses throughout the trial are defined as follows:

* Prescreening: preconsent (subject considering trial or study staff considering patient for the trial per institutional recruitment methods).
* Screening: period after consent, but prior to eligibility confirmation.
* Consented: consented, prior to eligibility confirmation.
* Eligible: the local investigator confirms all eligibly criteria apply.
* On study/enrolled: date eligibility is confirmed.
* On arm: date of enrollment.
* On treatment: first day treatment was given to the last day treatment was given.
* Off treatment: the last day treatment was given.
* On follow-up: from last day of treatment to the end of follow-up period.
* Off study: follow-up period completed, with no additional data gathered.
* Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off study by the local principal investigator.

## Prescreening and Screening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent, but are not subsequently assigned to the study intervention or enrolled in the study. MCWCC CTO will follow its SOPs regarding prescreening and screening tracking.

## Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians, and/or other IRB-approved recruitment methods. No study conduct, including subject prescreening, can occur until after IRB approval.

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

## Screening Procedures

Refer to study calendar of events.

Screening assessments must be performed within **<<X>>>** prior to **<<X (eligibility confirmation, etc.>>**, with the exception of consent (may be obtained any time before study-specific procedures are obtained) <<and X procedures>> (<<within X of eligibility confirmation>>).

<<For women of childbearing potential, a negative pregnancy test must be obtained within <<X days>> prior to treatment.>>

Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window.

## **Eligibility Confirmation**

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.

## Eligibility Criteria

\*No waivers of protocol eligibility will be granted.

All inclusion and exclusion criteria should be explicitly stated as applying to the subject in the source material (e.g., “The patient has been postmenopausal since 2010”).

PURPOSE: This defines the study population. The specific criteria will serve as a list for the study team that enrolls the patients. It will leave no ambiguities for study personnel.

* Subject inclusion criteria. [GCP 6.5.1]
* Subject exclusion criteria. [GCP 6.5.2]
* Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial. [GCP 6.6.2] (See also the Section 5 TREATMENT PLAN)
* Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures for specifying: (a) when and how to withdraw subjects from the trial/investigational product treatment; (b) the type and timing of the data to be collected for withdrawn subjects; (c) whether and how subjects are to be replaced; and (d) the follow-up for subjects withdrawn from investigational product treatment/trial treatment. [GCP 6.5.3] (See also Section 5 TREATMENT PLAN; Section 11 STATISTICAL CONSIDERATIONS.)

*The following prompts are suggestions for inclusion and exclusion criteria. The prompts should be replaced with the actual criteria or deleted as is appropriate for the study.   
  
Patients must have baseline evaluations performed prior to the first study drug dose and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all study aspects, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.*

## Inclusion Criteria

*Criteria which might be included: (i) disease including histological or cytological confirmation and stage; (ii) allowable type and amount of prior therapy; time since last treatment; (iii) age restriction, if any; (iv) performance status and scale; (v) life expectancy; (vi) any organ or marrow function requirements; (vii) any laboratory parameter requirements; (viii) willingness to use contraception as required; (ix) any additional inclusion criteria that are appropriate to the study.*

*Create a numbered list of Inclusion and Exclusion Criteria — avoid using outline format or sub-items, such as 4.2.1., 4.2.2, etc.*

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

OR

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

*You may specify eligible disease(s)/stage(s) using the* [*CTEP Simplified Disease Classification*](http://ctep.cancer.gov/protocolDevelopment/codes_values.htm)]

2. *Provide appropriate criteria for the lesion measurement in this patient population. Lesions are either measurable or nonmeasurable, using the criteria provided in Section 9 Reporting and Documentation of Results. For example, “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 > 20 mm with conventional techniques or as > 10 mm with spiral CT scan, MRI or calipers by clinical exam. See Section 9 for the measurable disease evaluation methods.*

*OR*

*Provide 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)*](http://jco.ascopubs.org/content/17/4/1244.long)*; J Clin Oncol 8(5):813-19, 1990 (acute myeloid leukemia); and Blood 887(12):4990-97, 1996 (chronic lymphocytic leukemia).*

3. *State allowable type and amount of prior therapy. Define any limitations on prior therapy and the time from last prior regimen (e.g., no more than six cycles of an alkylating drug; no more than 450 mg/m2 doxorubicin for drugs with expected cumulative cardiotoxicity). Include separate definitions for duration as needed (e.g., at least four weeks since prior chemotherapy or radiation therapy, six 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).*

4. Age >18 years

5. *State any age and/or gender/race-ethnic restrictions.*

6. *State allowable type and amount of prior therapy.*

7. *State any life expectancy restrictions.*

8. *State whether ECOG or Karnofsky Performance Status will be employed (see Appendix 1 Performed Status Criteria).*

9. *State requirements for organ and marrow function, examples provided below:*

| **Organ and Marrow Function Table** | |
| --- | --- |
| **Adequate bone marrow function:** | |
| Hemoglobin | 8.0 g/dL |
| WBC | >4,000 |
| absolute neutrophil count | > 1,500/mcL |
| Platelets | >100,000/mm3 |
| **Adequate hepatic function:** | |
| total bilirubin | < 2 mg/dL |
| AST(SGOT)/ALT | < 5 times institutional upper limit |
| **Adequate renal function:** | |
| creatinine clearance | > 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal” |

10. Pregnancy

It is not known what effects this treatment has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet one of the following:

* Postmenopausal for at least one year before the screening visit, or
* Surgically sterile, or
* If they are of childbearing potential, agree to practice two effective methods of contraception from the time of signing of the informed consent form through three months after the last dose of study drug, AND
* Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, or
* Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable contraception methods.)

Male patients, even if surgically sterilized (i.e., status postvasectomy), must agree to one of the following:

* Practice effective barrier contraception during the entire study treatment period and through 90 days after the last study drug dose, OR
* Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
* Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

*State any requirements for pregnancy testing or birth control. For approved products, review package insert and follow the stated recommendations.*

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

12. *State any other appropriate inclusion criteria for this study.*

## Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

*Criteria which might be included: (i) receiving any other investigational agents; (ii) brain metastases, if a factor; (iii) history of allergic reactions to any of the required agents on the study; (iv) concomitant medications or substances that have the potential to affect the activity or pharmacokinetics of the study agent; (v) uncontrolled or intercurrent illness that would interfere with achieving the study objectives;(vi) pregnant; (vii) HIV-positive; (viii) any additional exclusion criteria that are appropriate to the study.*

*As noted, make sure that a statement regarding the concomitant medications that are permitted or prohibited is included and any requirements regarding the allowance of concurrent and prior malignancies are included.*

1. *State therapy restrictions, for example:*

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

2. *State restrictions regarding use of other investigational drugs.*

3. *State exclusion requirements due to comorbid disease or concurrent illness, for example:   
  
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.*

*4. State requirements regarding history of allergic reactions attributed to compounds of similar chemical or biologic composition to investigational drug or device.*

5. Patients receiving any medications or substances that are inhibitors or inducers of CYP450 enzyme(s) are ineligible. Lists of medications and substances known or with the potential to interact with the specified CYP450 enzyme(s) isoenzymes are provided in Appendix 2.

*State exclusion criteria relating to concomitant medications or substances that have the potential to affect the activity or pharmacokinetics of the study drug. Examples of drugs or substances include those that interact through the CYP450 isoenzyme system or other sources of drug interactions (e.g., P-glycoprotein). The above text (CYP450 interactions) may be used or modified.*

6. Pregnant women are excluded from this study because << study drug >> is a/an << drug class >> drug with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with << study drug >> breastfeeding should be discontinued if the mother is treated with << study drug >>.   
  
*If more than one study drug is administered:*If more than one study drug is administered These potential risks may also apply to other drugs used in this study.

*State the medical or scientific reason if pregnant or nursing patients will be excluded from the study. See CTEP’s* [*Guidelines Regarding the Inclusion of Pregnant and Breast-Feeding Women on Cancer Clinical Treatment Trials*](http://ctep.cancer.gov/protocolDevelopment/policies_pregnant.htm)*. Also, refer to the manufacturer’s package insert or Investigator Brochure for the study drugs that will be used. Some manufacturers may have their own language they want included in the protocol. The above text may be used or modified.*

7. *If applicable to your study:* HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with << study drug >>. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.  
  
*State the medical or scientific reason if patients who are cancer survivors or those who are HIV-positive will be excluded from the study. Refer to CTEP’s* [*Guidelines Regarding the Inclusion of Cancer Survivors and HIV-Positive Individuals on Clinical Trials*](http://ctep.cancer.gov/protocolDevelopment/policies_hiv.htm)*. The above text may be used or modified.]*

8. *Insert any other drug-specific exclusion criteria*

*“I have reviewed all inclusion and exclusion criteria and confirm the subject is eligible.”*

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(Local Investigator Signature and Date)

## 4.9 Enrollment

Subject enrollment logistics are defined as follows:

* OnCore® enrollment entry must occur within 24 hours of eligibility confirmation.
* A case/subject/sequence number is assigned in OnCore® from the MCW staff in sequence (i.e., inputted from the site staff, not generated by OnCore®).
  + Sites enter the case number according to the following template “XXX-XXX-001” or “XXX-001” (unless otherwise specified by MCW OnCore® Staff), where the “XXX” sections are abbreviations are determined by MCW OnCore® Staff, and “001” is the sequential subjects who consented to the trial at the site (e.g., the first enrolled case number would be XXX-XXX-001, but the second would be XXX-XXX-002).

## 4.10 Treatment

Treatment must start within <<X seven days of enrollment>>.

<< For women of childbearing potential, a negative pregnancy test must be obtained within seven days prior to treatment.>>

If unforeseen issues occur and treatment is delayed after enrollment, the MCW PI must provide approval to continue treatment outside the seven-day window. The MCW PI will consider if any procedure for safety should be repeated, or if the subject should be discontinued from the trial. Subjects who sign the informed consent form and are enrolled but do not receive the study intervention <<may or may not>> be replaced.

Refer to calendar of events and dose modification section for treatment parameters.

<<If procedures are complicated in nature, detail them in the following manner.>>

**Screening**

The screening procedures and assessments must be completed within << #/time frame >> of the <<X>>.  
  
*(or the first day of study drug/infusion.)*

* Physical examination
* Vital signs
* Complete medical history
* Baseline conditions assessment
* Documentation of disease assessment (disease-specific staging criteria)
* Performance status (ECOG, KPS, etc.)
* Measurable disease

*Disease Assessment/Measurable Disease/Imaging — these are listed as different items, as required for OnCore® calendar/IRB/billing configuration. Edit these procedures accordingly for your study.*

* History of prior treatments and any residual toxicity relating to prior treatment
* Baseline medications taken within << # >> days of Day 1
* Sample of tumor tissue *[describe details of sample required, if a biopsy is needed]*
* Hematology labs (other than CBC with differential)
* Complete blood count (CBC) with differential and platelet count
* Blood chemistry assessment, including:   
    
  **A)** Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH), fasting lipid panel (low-density lipoprotein [LDL], total cholesterol, triglycerides).   
  **B)** Thyroid function tests: thyroid-stimulating hormone (TSH), free thyroxine (FT4).
* Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
* Tumor marker assessments *[such as CAE, AFP, CA19-9, CA 125, etc.]*
* Immune parameter assessments *[such as immunoglobulins, etc.]*
* Serum hepatitis assessment, including hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C virus RNA
* Urinalysis
* Serum or urine pregnancy test within << #/time frame >> prior to the start of study drug
* Imaging (CT or MRI) of << body locations >> for tumor/lesion assessment
* Electrocardiogram (ECG)
* Cardiac assessment (ECHO, MUGA, etc.)
* Bone scan
* Specimen collection for banking *(blood, tissue, etc.)*
* Biopsy
* Questionnaires  
    
  *[NOTE: Please provide a window for scans, e.g: “Only to be performed if ≥ X weeks since the last scan.” Adjust time frame window for completing scans appropriately – most scans need a 28-day window, while other procedures, such as labs and ECG/EKG need about seven days to complete. Modify the procedures and assessments list as needed.*

**Study Procedures Cycle << # >>, Day << # >>**  
  
These procedures must be completed within << #/time frame >> of Day << # >>.

* Evaluation of clinical response or deterioration
* Physical examination
* Vital signs
* Performance status
* Evaluation of adverse events
* Concomitant medications
* Hematology assessment, including CBC with differential and platelet count
* Blood chemistry assessment, including:  
     
  **A)** Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel  
  **B)** Thyroid Function Tests: TSH, FT4
* Coagulation assessment, including PT/PTT/INR
* Tumor marker assessments *[such as CAE, AFP, CA19-9, CA 125, etc.]*
* Immune parameter assessments *[such as immunoglobulins, etc.]*
* Urinalysis
* Serum or urine pregnancy test
* Imaging (CT or MRI) of << body locations >> for tumor/lesion assessment
* Electrocardiogram (ECG)
* Cardiac assessments (ECHO, MUGA, etc.)
* Bone scan
* PK/PD/PG
* Biopsy

**End of Treatment Procedures**  
  
To be completed within 30 days of the last dose of the study drug.

* Evaluation of clinical response or deterioration
* Physical examination
* Vital signs
* Performance status
* Evaluation of adverse events
* Concomitant medications
* Hematology assessment, including CBC with differential and platelet count
* Blood chemistry assessment, including:   
    
  **A)** Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel  
  **B)** Thyroid function tests: TSH, FT4
* Coagulation assessment, including PT/PTT/INR
* Tumor marker assessments  *[such as CAE, AFP, CA199, CA 125, etc.]*
* Immune parameter assessments  *[such as immunoglobulins, etc.]*
* Urinalysis
* Serum or urine pregnancy test
* Imaging (CT or MRI) of << body locations >> for tumor/lesion assessment
* Electrocardiogram (ECG)
* Bone scan
* PK/PD/PG
* Questionnaires

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

* Evaluation of clinical response or deterioration
* Physical examination
* Vital signs
* Performance status
* Evaluation of adverse events
* Concomitant medications
* CBC with differential and platelet count
* Hematology labs (other than CBC with differential)
* Blood chemistry assessment, including:   
    
  **A)** Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel;   
  **B)** Thyroid function tests: TSH, FT4
* Coagulation assessment, including PT/PTT/INR
* Tumor marker assessments *[such as CAE, AFP, CA19-9, CA 125, etc.]*
* Immune parameter assessments *[such as immunoglobulins, etc.]*
* Urinalysis
* Serum or urine pregnancy test
* Imaging (CT or MRI) << body locations >> *(scans would only be completed in follow-up for patients whose disease has not yet progressed since entering the study)*
* Electrocardiogram (ECG)
* Cardiac assessment (ECHO, MUGA, etc.)
* Bone scan

## 4.11 Discontinuation of Study Treatment, Withdrawal, and Compliance

Discontinuation from the study treatment does not mean discontinuation from the study. Subject will be considered in follow-up, study procedures should still be completed as indicated by the study protocol and AEs/SAEs will continue to be reported according to this protocol.

In the absence of treatment delays due to adverse events, study treatment/intervention may continue until:

* Disease progression.
* General or specific changes in the subject’s condition renders the subject unacceptable for further treatment in the investigator’s judgment.
* Intercurrent illness that prevents further treatment administration.
* Subject decides to withdraw from the study.
* The subject has significant noncompliance with the protocol (see below).
* Unacceptable adverse event(s) and/or dose level reduction beyond requirements as detailed in this protocol.
* Study stopping rules are met.

Subjects who sign the informed consent form, and are enrolled and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study, <<will or will not>> be replaced.

**Consent Withdrawal**

A subject may decide to withdraw from the study at any time. MCWCC CTO will follow its IRB of record’s SOPs regarding consent withdrawal.

If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal with no study follow-up.

- Selective consent withdrawal from interventional portion of the study, but agree to continued follow-up of associated clinical outcome information.

**Investigator-initiated Withdrawal**

The investigator will withdraw a subject whenever continued participation is no longer in the subject’s best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject’s request to end participation, a subject’s noncompliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

**Subject Compliance**

<<FOR ORAL MEDICATAIONS: Subjects should be instructed to return their pill bottles (including any unused medication) and medication diary to the site at each visit that has a physical exam (according to the calendar of events) for tablet count and reconciliation.>>

<<The study team should check for percent adherence/compliance during the previous period on the medication diary and reconcile the information with the pills returned by the subject.>>

<<If a subject does not meet 80% compliance during the previous cycle, the study team should re-educate the subject on the importance of compliance and document the encounter. If this is an ongoing issue then the MCW principal investigator should determine whether the subject should continue on trial.>>

## 4.12 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

* The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the participant.
* A participant is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occurs at two consecutive scheduled protocol calendar timepoints:
  + Three telephone calls (at least one day apart) from the study team are unanswered

**AND**

* + A letter to the participant’s last known mailing address goes unanswered (refer to Appendix 4 for a template).

**AND**

* + These contact attempts must be documented in the participant’s medical record or study file.
* Update OnCore® (follow-up tab and eCRF) when a participant is officially considered lost to follow-up.
* If a subject is considered lost to follow-up, but subsequently contacts the participating site study team, the subject should be considered in follow-up again.

## 4.13 Accrual Suspension and Closure

The MCW PI facilitates the suspension and closing of accrual in the following manner:

* OnCore® tracks accrual throughout the study.
* If the study must be suspended, OnCore® is updated to a ‘suspended’ status.
* When the accrual number is reached, OnCore® notifies staff of study closure.

## 4.14 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the calendar of events or has been discontinued.

## 4.15 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study principal investigator, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the investigational new drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) will promptly inform the MCW Institutional Review Board (IRB) and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

# Treatment Plan

PURPOSE: To describe the treatment and how it will be administered.

* A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packing, and labeling of the investigational product(s). [GCP 6.4.4] (See also Section 8 PHARMACEUTICAL INFORMATION.
* The expected duration of the subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any. [GCP 6.4.5]
* The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial. [GCP 6.6.1]
* Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial. [GCP 6.6.2] (See also Section 4 PATIENT SELECTION.)
* Procedures for monitoring subject compliance. [GCP 6.6.3]
* Specification of safety parameters. [GCP 6.8.1] (See also Section 6 DOSING DELAYS/DOSE MODIFICATIONS; Section 7 ADVERSE EVENTS.)
* The methods and timing for assessing, recording, and analyzing safety parameters. [GCP 6.8.2] (See also Section 7 ADVERSE EVENTS; Section STUDY CALENDAR; Section 11 STATISTICAL CONSIDERATIONS; Section 12 DATA AND SAFETY MONITORING PLAN.)
* The type and duration of the follow-up of subjects after adverse events. [GCP 6.8.4]

## Investigational Agent Administration (or other appropriate title; “Radiation Therapy” might be appropriate for a radiation oncology protocol)

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

*Use footnotes to specify the drug order. If a specific order is not necessary, please indicate this. Investigators should state if this is standard of care. Investigators should also consult with a pharmacist (inpatient), TRU nurse and inpatient nurse or staff, if necessary.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Regimen Description | | | | | |
| Study Drug | **Premedication; precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Study Drug 1 | Premedicate with << drug >> for << # >> days prior to Study Drug 1 | 100 mg | Oral | Days 1-3 week 1 | 4 weeks (28 days) |
| Study Drug 2 | Avoid exposure to cold (food, liquids, air) for 24 hr after each dose | 300 mg/m2 | Intravenous | Days 1-3 week 1 |
| Study Drug 3 | Take with food | 50 mg tablet | Oral | Daily,  weeks 1 and 2 |
| Footnotes | | | | | |

## Dose Escalation Schedule

\*\*’\*PHASE 1 STUDIES\*\*\*

*For phase 1 dose-escalation studies, state the starting study drug dose and describe the dose-escalation scheme and treatment regimen (dose, route, duration of infusion for intravenous drugs and schedule). Use exact dose rather than percentages. State any special precautions or warnings relevant for agent administration (e.g., incompatibility of agent with commonly used intravenous solutions, necessity of administering agent with food, premedications, etc.). A table may be used to describe the regimen.*

*Describe the number of patients to be treated at each level and how a decision about dose escalation or expansion of cohort sizes will be made. If there are multiple study drugs being used in the study, include dose escalation for each study drug. Escalation of only one drug at each dose level is recommended.*

*\*\*\*PHASE 2 STUDIES\*\*\**

*Describe the regimen (agent, dose, route, duration of infusion for intravenous drugs and schedule) and state any special precautions or warnings relevant for investigational study agent administration (e.g., incompatibility of the agent with commonly used intravenous solutions, necessity of administering agent with food, premedications, etc.). Inclusion of a treatment table may be useful in clarifying the regimen.*

*\*\*\*INTERVENTIONAL STUDIES INVOLVING OTHER THAN A STUDY DRUG\*\*\**

*If the primary intervention involves something other than a study drug, a different header will most likely be more appropriate for this section. As an example, “Radiation Therapy” may more accurately reflect the intervention. The “Additional Treatment Modalities” section might then be used to describe the concomitant use of other treatment modalities.*

| Dose Escalation Schedule | | |
| --- | --- | --- |
| Dose Level | **Dose of Study Drug\*** | **Minimum Number of Patients** |
| -1 |  | 3 |
| 1 |  | 3 |
| 2 |  | 3 |
| 3 |  | 3 |
| \*Footnotes: State exact dose in units (mg/m2, µ/kg, etc.) rather than as a percentage | | |

## Dose-Limiting Toxicity (DLT) and Maximum-Tolerated Dose (MTD)*.*

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

|  |  |
| --- | --- |
| Number of Patients with DLT at a Given Dose Level | Escalation Decision Rule |
| 0 out of 3 | Enter three patients at the next dose level. |
| > 2 | Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only three patients were treated previously at that dose. |
| 1 out of 3 | Enter at least three more patients at this dose level.   * If zero (0) of these three patients experience DLT, proceed to the next dose level. * If one or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only three patients were treated previously at that dose. |
| <1 out of 6 at highest dose level below the maximally administered dose | This is generally the recommended phase 2 dose. At least six patients must be entered at the recommended phase 2 dose. |

*Provide definition of types, grades and duration of AEs that will be considered dose-limiting toxicities, or provide definitions of other endpoints that will be used to determine dose escalations. Note any definite exclusions from the DLT definition (if any rule states any grade 3/4 hematologic toxicity is a DLT but this excludes lymphopenia of any grade) and include when the DLT will be determined and give the specific timeframe for DLT evaluation (first cycle of therapy, any time during treatment, etc.). Please also describe how you will determine the MTD/recommended Phase 2 dose. This section must be consistent with the Section 11 Statistical Considerations and Section 6 Dosing Delays/Dose Modifications.*

*State any special warnings or precautions relevant to study drug administration, for example, incompatibility of study drug with commonly used intravenous solutions, necessity of administering drug with food, premedications, hydration, whether any monitoring of vital signs during or shortly after treatment is required, etc. If treatment will be self-administered (oral drug or self-injection), please reference any patient tools that will be implemented (study medication diary, subcutaneous injection instruction sheets, etc). State how missed (or vomited) doses should be handled.*

* + 1. **Dose-Limiting Toxicity**

Management and dose modifications associated with the AEs are outlined in Section 6 Dosing Delays/Dose Modifications.

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

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

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

*[repeat as necessary]*

*State the definition of the major potential toxicity and type, and how it will be managed and for how long. State how it will be graded and at what point the patient will be removed from study for dose-limiting toxicity related to << type >>. Describe DLT attribution, if necessary.*

*Describe any grading relative to supportive care, such as any nausea grade 3, or nausea that persists despite optimal supportive care; mouth sores, diarrhea, etc.*

## Additional Treatment Modalities

*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, not as study assessments. If this study involves no other modalities or procedures, state “No other modalities will be used in this study.” Study assessments are defined and/or listed in Section 5 and the Study Calendar .*

## General Concomitant Medication and Supportive Care Guidelines *(if applicable)*

*Describe in detail any prophylactic or supportive care regimens required for investigational study agent(s) administration and state any special precautions or relevant warnings (e.g., incompatibility of agent with commonly used intravenous solutions, necessity of administering agent(s) with food, premedications, etc.). Provide the same information for any other agent used in the study.*

*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. Note: This is also mentioned in Section 4.*

*Precautions or prohibitions regarding herbal products, complementary or alternative medications and dietary supplements should be included here.*

* + 1. **Usage of Concurrent/Concomitant Medications**  
         
       *Complete this section as required for the particular study and drug interactions concerns, for example consider:*
* *Temperature elevations and treatment*
* *Growth factors*
* *Antidiarrheals*
* *Antiemetics*
* *Drugs such as lorazepam, prochlorperazine or serotonin antagonists may be used if clinically indicated*
* *Antihistamines*
* *Topical Steroid Creams*
* *Anticoagulants*

*Include any specific reasons for this indication or treatment.*

* + 1. **Dietary Restrictions**

**5.5.3 Prohibited Medications***Include any prohibited medications that are specific to the drugs in this study. A standard list of prohibited medications is provided in Appendix 2.*

## Monitoring Subject Compliance *(if applicable)*

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Comprehensive instructions will be provided to the patient in order to ensure compliance with dosing procedures.

*For orally or self-administered drugs, provide a method for assessing compliance with treatment, for example:*

*“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 << time frame >>.”*

*The use of a diary should also be included in the schedule of procedures and study assessments.*

## Follow-up Period

*Describe how and for how long the patients will be followed after an AE or after the completion of the treatment phase of the study. The details may be placed in Study Calendar, with an appropriate reference made to that section of the protocol. Sample language follows:*

Patients will be followed for # weeks/months/years after removal from the study treatment or until death, whichever occurs first.

Patients removed from the study treatment for unacceptable SAEs will be followed until resolution or stabilization of the adverse event. SAEs will be followed until completion.

# Dosing Delays/Dose Modifications

PURPOSE: To outline treatment modifications and management of specific toxicities and adverse events.

* Specification of safety parameters. [GCP 6.8.1] (See also Section 5 TREATMENT PLAN; Section 7 ADVERSE EVENTS.)

*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 is provided as an example and can be modified, replaced or deleted as appropriate.*

*See the below examples.*

Patients must meet eligibility criteria eligible on Day 1 to be treated. The below sample table is for an orally available drug.   
  
*Sample language: Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.*

|  |  |  |
| --- | --- | --- |
| Dose Modifications and Dosing Delays | | |
| **Dose Level** | | **Dose of Study Drug** |
| -1 | |  |
| 1 | |  |
| 2 | |  |
| 3 | |  |
| Footnotes | | |
| **Example:        Ixazomib and Bendamustine Dose Adjustments for Hematologic Toxicities** | | |
| Criteria | | Action |
| Within-Cycle Dose Modifications | |  |
| * If platelet count ≤ 30 X 109/L or ANC ≤ 0.50 X 109/L on a ixazomib dosing day (other than Day 1) | | * Study treatment should be withheld. * Complete blood count (CBC) with differential should be repeated until the ANC and/or platelet counts have exceeded the prespecified values (see Table 6-1) on at least 2 occasions. * Upon recovery, bendamustine may be reinitiated with 1 dose level reduction and upon recurrence of same toxicity  lower ixazomib  dose  to  1 dose level. |
| Dose Modifications for Subsequent Treatment Cycles | |  |
| * Delay up to 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Table 6-1 * ANC < 1.0 X 109/L, platelet count < 75 X 109/L, or other nonhematologic toxicities > Grade 1 or not to the patient’s baseline condition | | * Hold both drugs until resolution as per criteria Table 6-1. * Upon recovery, reduce  bendamustine first and then ixazomib to 1 dose level. * The maximum delay before treatment should be discontinued will be > 2 weeks or at the discretion of the PI. |
| Dose Modifications for Subsequent Treatment Cycles | |  |
| * All hematologic toxicities | | * For hematologic toxicity that occurs during a cycle but recovers in time for the start of the next cycle: * If dose was reduced for bendamustine or ixazomib within the cycle, start the next cycle at that same dose. * If due to toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib only by 1 dose level at the start of that cycle. * Do not reduce the dose both within a cycle and at the start of the next cycle for the same toxicity. |

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Event Version 5.

*All treatment modifications must be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose. Dose modifications/treatment delays for study drug(s) may be presented separately or together. Table format is recommended.*

*Below are dose modification tables for the following AEs: nausea, vomiting, diarrhea, neutropenia and thrombocytopenia; and a template (blank) dose modification table. Note 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.*

|  |  |  |
| --- | --- | --- |
| Adverse Event: Nausea | | |
| Grade of Event | **Management/Next Dose for << study drug >>** | **Management/Next Dose for << study drug >>** |
| ≤ Grade 1 | No change in dose | No change in dose |
| Grade 2 | Hold until ≤ Grade 1  Resume at same dose level | Hold until ≤ Grade 1  Resume at same dose level |
| Grade 3 | Hold\* until < Grade 2  Resume at one dose level lower, if indicated\*\* | Hold\* until < Grade 2  Resume at one dose level lower, if indicated\*\* |
| Grade 4 | Off protocol therapy | Off protocol therapy |
| Recommended management: antiemetics. | | |
| \*Patients requiring a delay of > 2 weeks should go off protocol therapy  \*\*Patients requiring > two dose reductions should go off protocol therapy | | |
|  | | |

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

|  |  |  |
| --- | --- | --- |
| Adverse Event: Vomiting | | |
| Grade of Event | **Management/Next Dose for << study drug >>** | **Management/Next Dose for << study drug >>** |
| ≤ Grade 1 | No change in dose | No change in dose |
| Grade 2 | Hold until ≤ Grade 1  Resume at same dose level | Hold until ≤ Grade 1  Resume at same dose level |
| Grade 3 | Hold\* until < Grade 2  Resume at one dose level lower, if indicated\*\* | Hold\* until < Grade 2  Resume at one dose level lower, if indicated\*\* |
| Grade 4 | Off protocol therapy | Off protocol therapy |
| Recommended management: antiemetics. | | |
| \*Patients requiring a delay of > 2 weeks should go off protocol therapy  \*\*Patients requiring > two dose reductions should go off protocol therapy | | |

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

|  |  |  |
| --- | --- | --- |
| Adverse Event: Neutropenia | | |
| Grade of Event | **Management/Next Dose for << study drug >>** | **Management/Next Dose for << study drug >>** |
| ≤ Grade 1 | No change in dose | No change in dose |
| Grade 2 | Hold until ≤ Grade 1  Resume at same dose level | Hold until ≤ Grade 1  Resume at same dose level |
| Grade 3 | Hold\* until < Grade 2  Resume at one dose level lower, if indicated\*\* | Hold\* until < Grade 2  Resume at one dose level lower, if indicated\*\* |
| Grade 4 | Off protocol therapy | Off protocol therapy |
| << Insert any recommended management guidelines >> | | |
| \*Patients requiring a delay of > 2 weeks should go off protocol therapy  \*\*Patients requiring > two dose reductions should go off protocol therapy | | |
|  | | |

|  |  |  |
| --- | --- | --- |
| Adverse Event: | | |
| Grade of Event | **Management/Next Dose for << study drug >>** | **Management/Next Dose for << study drug >>** |
| ≤ Grade 1 |  |  |
| Grade 2 |  |  |
| Grade 3 |  |  |
| Grade 4 |  |  |
| << Insert any recommended management guidelines >> | | |
| \*Footnote any relevant guidelines regarding how long a delay in therapy is allowed before patients should go off protocol therapy  \*\*Footnote any relevant guidelines regarding how many dose reductions are allowed before patients should go off protocol therapy | | |

## Monitoring and Toxicity Management

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

Each patient will be assessed periodically for any toxicity development. Toxicity will be assessed according to the NCI CTCAE v5.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

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

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

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

## Other Toxicities

(Also see Section 7 Known AEs List)

|  |  |
| --- | --- |
| Cardiovascular toxicity | A major potential toxicity with << study drug >> is << AE >> which will also be graded on the basis of the NCI CTCAE v5.0 scale |
| Hematologic toxicities | << State any toxicities specific to study drug(s), as applicable >> |
| Viral Infection | << State any toxicities specific to study drug(s), as applicable >> |
| Gastrointestinal toxicity | << State any toxicities specific to study drug(s), as applicable >> |
| << insert as needed >> |  |
| << insert as needed >> |  |

***Examples:***

***Hematologic Toxicity***

*On the day of starting each cycle, neutrophil and platelet hematologic parameters must have resolved to baseline or grade 1. If these criteria are not met, therapy will be held by one-week increments for a maximum of four weeks. If treatment cannot be given during that time frame, the patient will be removed from study. Any grade 4 hematologic (neutropenia, anemia, and thrombocytopenia) toxicity will result in a dose reduction. In the event of ANC nadir <500/mm3, hemoglobin <6.5g/dL, or platelets nadir <25,000/mm3, reduce the fludarabine to 25 mg/m2 administered only on days one to three. Treatment can resume after allowing recovery to the pretreatment criteria. Should the patient develop a recurrent grade 4 hematologic toxicity, a second dose reduction to fludarabine 15 mg/m2 administered only on days one to three will be required. Treatment can resume after allowing recovery to the pretreatment criteria assuming that fludarabine and methoxyamine administration has not been delayed for more than four weeks. Otherwise, the study drugs must be discontinued (see Criteria for Discontinuation of Study Drug, section \_\_\_.)*

***Non-Hematologic***

*Toxicity Grade 3/4 non-hematologic toxicity (except fatigue, or anorexia lasting < 7 days or Grade 3 nausea and/or vomiting that persists for < 2 days following appropriate supportive care) that is drug related must return to a grade 1 or better. If these criteria are not met, therapy will be held by one week increments for a maximum of four weeks. If treatment cannot be given during that time frame, the patient will be removed from study. Following resolution of the toxicity to grade 1 or better, toxicities deemed related to fludarabine will require dose reduction to 25 mg/m2 x 3d. For toxicities felt to be related to methoxyamine, dose reduction to one dose level lower is required for further therapy. In the case of recurrence of the specific grade 3/4 non-hematologic toxicity, the patient should be removed from study.*

*All scheduled visits will have a ±3-day window with the exception of cycle 1 week 1 given the need for exact timing of correlative studies.*

***Examples for Radiotherapy:***

**Radiotherapy Dose Modifications for In-field Non-Hematologic Toxicities**

*Radiation treatment will be interrupted for grade 4 in-field toxicity and/or grade 4 neutropenia with fever. Aggressive supportive care is encouraged throughout the course of radiotherapy. If the patient is near completion of therapy, then every attempt should be made to complete treatment despite acute toxicity. Otherwise, treatment should be restarted when the accompanying toxicity declines to ≤ grade 2. If treatment is interrupted for more than three weeks due to non-hematologic toxicity, remove the patient from protocol treatment.*

**Provide a treatment modification table for In-Field Non-Hematologic Toxicities.**

# Adverse Events: Definitions, Collection, and Reporting Requirements

## Definitions

### **Adverse Event (AE)**

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonisation [ICH], E2A, E6).

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

<https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

### **Serious Adverse Event (SAE)**

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

* **Death.** Results in death.
* **Life-threatening**. Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
* **Hospitalization**. Requires inpatient hospitalization ≥24 hours or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).
* **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person’s ability to conduct normal life functions).
* **Pregnancy**
* **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

### **Attribution of an Adverse Event**

An assessment of the relationship between the adverse event and the medical intervention, using the following categories:

**Definitely Related**: *The AE is clearly related to the intervention*. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

**Probably Related:** *The AE is likely related to the intervention.* There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

**Possibly Related:** *The AE may be related to the intervention.* There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject’s clinical condition, other concomitant events).

**Unlikely:** *The AE is doubtfully related to the intervention.* A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject’s clinical condition, other concomitant treatments).

**Unrelated:** *The AE is clearly NOT related to the intervention.*The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.

### **Expectedness of an Adverse Event**

Study Investigator or treating Physician will be responsible for determining whether an AE is expected or unexpected as indicated in the protocol, informed consent form and/or drug information brochure. An AE will be considered unexpected if the nature, severity, or frequency of the event is NOT consistent with the risk information previously described for the study intervention.

## Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

### **Collection of Adverse Events**

All (or specify if only certain grade AE needed) adverse events (including SAEs) must be recorded in OnCore® and/or an adverse event log. All AEs required to be collected must be graded according to the CTCAE v5. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Investigator’s or Treating physician’s assessment of AE attributions must also be documented.

AEs will be collected from the time the subject signs the consent form through 30 days post last dose of study drug(s). AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early). All adverse events collected per the protocol will be followed with appropriate medical management until they are resolved, if they are related to the study treatment, or until the investigator deems the event to be chronic.

Please see Section 7.2.2 and Table 7.2.2 to identify the adverse events that need to be reported.

### **Reporting of Adverse Events and Serious Adverse Events**

Please refer to Table 7.2.2 below to identify adverse events that meet reporting requirements.

All SAEs that occur after the subject has signed the consent form through 30 days post last dose of study drug(s) will be reported. All SAEs will be followed until satisfactory resolution, or until the investigator deems the event to be chronic.

All SAEs must also be documented in OnCore®.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Attribution** | **SAE** | | | | **AE** | | |
| **Grade 1, 2 & 3** | | **Grade 4 and 5** | | **Grade 3** | **Grade 4** | |
| **Expected** | **Unexpected** | **Expected** | **Unexpected** | **Unexpected** | **Expected** | **Unexpected** |
| **Unrelated**  **Unlikely** | **IRB1 and DSMC- Routine Review2**  **Sponsor6** | **IRB1 and DSMC- Routine Review2** | **IRB1- Routine Review2**  **DSMC3-Within 5 calendar days**  **Sponsor6** | **IRB1- Routine Review2**  **DSMC3-Within 5 calendar days** | **DSMC2- Routine Review** | **DSMC-**  **Heme: Routine review2,4**  **Non-Heme:**  **Within 5 calendar days3** | **DSMC3-**  **Within 5 calendar days** |
| **Possible**  **Probable**  **Definite** | **IRB1 and DSMC3- Within 5 calendar days**  **FDA5**  **Sponsor6** | **IRB1 and DSMC3- Within 5 calendar days**  **FDA5**  **Sponsor6** |

**Table 7.2.2**

1Guidance on Adverse Event Reporting to the IRB is available online at [MCW IRB Policies and Procedures.](http://www.mcw.edu/hrpp/policiesprocedures.htm)

2For routine reporting, the events will be reported to IRB as part of the annual continuing progress report, and the DSMC will review events entered in OnCore® at the time of scheduled monitoring.

3For expedited DSMC reporting, study coordinator/research nurse must notify the DSMC via email. For AEs, include the subject ID, date of event, grade, relatedness, expectedness, and a short narrative. For SAEs, DSMC will review the SAE report entered into OnCore®.

4Expected hematological grade 4 adverse events will be routine reported.

5Fatal or life-threatening SAEs meeting the criteria indicated in the above table will be reported to FDA no later than seven calendar days after study staff’s initial awareness of the event. If the SAE is not fatal or life-threatening and meets the above criteria, the timeline for submitting an IND safety report to FDA is no later than 15 calendar days after study staff’s initial awareness of the event. See Section 7.2.3 for detailed reporting instructions.

6If sponsor/drug manufacturer windows apply, add these to the table as well and include this footnote: See Section 7.2.3 for sponsor/drug manufacturer reporting instruction details.

### **Reporting Instructions**

* Food and Drug Administration **(**only if the study is being conducted under an IND)

An IND safety report will be submitted for any adverse event that meets all three definitions: possibly related to the study drug, unexpected, and serious. If the adverse event does not meet one of the above definitions, it should not be submitted as an expedited IND safety report.

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

*Suggested Reporting Form:*

US FDA MedWatch 3500A: <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>

* Sponsor/drug manufacturer providing Study Drug (If applicable)

[Add specific company/grantor requirements, when applicable]

*At MCW Cancer Center CTO’s request, please include the following language if working with a specific company/grantor:*

In addition to institutional and federal guidelines and per drug manufacturer requirements, all SAEs that occur after the subject has signed the consent form through 30 days post last dose of study drug(s) will be reported within 24 hours of study staff awareness (or in the case of a weekend or holiday, next business day), using OnCore®, which is to be entered in the SAE tab.

(Include reporting instructions, i.e., fax number, email, etc.)

## Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the [Human Research Protection Program website](http://www.mcw.edu/hrpp/InvestigatorsandStudyStaff.htm).

## Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

A product complaint is a verbal, written or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the drug manufacturer and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a drug manufacturer representative. Product complaints in and of themselves are not reportable events. If a product complaint results in an SAE, an SAE form should be completed.

# Pharmaceutical Information

* A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s). [GCP 6.4.4] (See Section 5 TREATMENT PLAN.)
* Accountability procedures for the investigational product(s), including the placebo(s) and the comparator(s), if any. [GCP 6.4.7]

*Each investigational or commercial agent should have its own section. The level of detail needed is dependent upon whether the agent is investigational or commercial. Refer to the investigator’s brochure, pharmaceutical data sheet, and/or package insert for this information. The source of information should be included in this section.*

## Agent #1 *(replace header with appropriate information; repeat this section as needed for each investigational or commercial agent)*

### **Product Description**

*[Refer to the package insert(s) for complete information.]*

<< Drug No. 1 >> is available in << # >> capsules/tablets for oral administration. *Include the available dosage forms, ingredients, and packaging as appropriate.*

**Classification:**

**Mechanism of Action:**

**Metabolism:**

**Contraindications:**

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

### **Solution Preparation**

*Describe how a dose is prepared. Include reconstitution directions and directions for further dilution, if appropriate.*

### **Investigational Agent Administration**

### **Storage Requirements**

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

### **Stability**

*Include the stability of the original dosage form, reconstituted solution and final diluted product as applicable.*

### **Route of Administration**

*Include a description of the method to be used and the rate of administration, if applicable.*

### **Nursing Implications**

### **Handling**

Drug No. 1 is stored at << >>.

*Example:* 25°C (77°F).

*Example:* Drug No. 2 in the single-use vial is stable at 2°C-8°C (36°F-46°F). Solutions diluted for infusion may be stored at 2°C-8°C (36°F-46°F) for 24 hours.

*Include any special handling requirements including the need for handling precautions or special equipment.*

### **Availability**

*Include the supplier of the agent and how the agent will be distributed to investigators.*

### **Agent Ordering**

*Describe how the agent will be obtained. If a multicenter study, indicate that each* ***site is responsible for ordering its own supply.***

*Example:*MCW will obtain << study drug >> directly from pharmaceutical company as study supply.

### **Agent Accountability**

*Describe how agent accountability records will be kept. The following text is modified from the CTEP model protocols and can be used or further modified as appropriate:*

*Example:* The Investigational Pharmacist will manage drug accountability records.

*Example:* The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from drug source using the Drug Accountability Record Form**.**

### **Agent Destruction and Return**

*Describe how any unused agent will be destroyed or returned to the supplier. Sample text:*

At the conclusion of the study, any unused agent will be destroyed according to institutional policies. The destruction will be recorded on the *Drug Accountability Record Form.*

# Reporting and Documenting Results (Measurement of Effect)

* Specification of the efficacy parameters. [GCP 6.7.1]
* Methods and timing for assessing, recording, and analyzing of efficacy parameters. [GCP 6.7.2] (See also STUDY CALENDAR; Section 11 STATISTICAL CONSIDERATIONS.)

*Provide the response criteria for the study. Separate documents are available with RECIST criteria for solid tumors, as well as additional criteria for hematologic malignancies.*Adverse event information and reporting is in Section 7.

## Evaluation of Efficacy (or Activity)

## Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors ([RECIST](http://jnci.oxfordjournals.org/content/92/3/205.full)) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria (or [International Workshop on Chronic Lymphocytic Leukemia [IWCLL]](http://bloodjournal.hematologylibrary.org/content/111/12/5446.full)).

#### **Definitions Evaluable for toxicity** All patients will be evaluable for toxicity from the time of their first study drug treatment.

**Evaluable for objective response**

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

#### **Disease Parameters**

*Include the response assessments that you are using (e.g., Cheson, et al., RECIST, etc.).* **Measurable disease**   
Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm), 10-mm caliper measurement by clinical exam (when superficial), and/or 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).  
  
All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered nonmeasurable except in cases of documented progression of the lesion since the completion of radiation therapy.

**Target lesions**

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

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

**Nonmeasurable disease (Tumor Markers)**Nonmeasurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all nonmeasurable (e.g., PSA, CA-125, CA19-9, CEA).

### **Methods for Evaluation of Measurable Disease**

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment. Please refer to the table of events.

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

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

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

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

### **Response Criteria**

*Add your definitions as appropriate.*

**Evaluation of Target Lesions**  
Complete Response (CR)  
Disappearance of all target lesions, determined by two separate observations conducted not less than four weeks apart. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). There can be no appearance of new lesions.  
  
Partial Response (PR)At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Stable Disease (SD)  
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

**Evaluation of Nontarget lesions**  
Complete Response (CR)

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

Incomplete Response/Stable Disease (SD)

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

**Evaluation of Best Overall Response**

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

| Response Criteria | | | | |
| --- | --- | --- | --- | --- |
| **Target Lesions** | **Nontarget Lesions** | **New Lesions** | **Overall Response** | **Best Response for this Category Also Requires** |
| CR | CR | No | CR | > 4 weeks confirmation |
| CR | Non-CR/ Non-PD | No | PR | > 4 weeks confirmation |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD | documented at least once > 4 weeks from baseline |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD\* | Yes or No | PD |
| Any | Any | Yes | PD |
| \* In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression | | | | |

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

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

**Duration of Response**

*This is optional text.*

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

Duration of stable disease

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

Progression-Free Survival

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

## Antitumor Effect – Hematologic Tumors

***Add information relevant to your work.***

**Primary Efficacy/ Response Assessment**  
Clinical response following three cycles of treatment. If patient is clinically in CR (without or with cytopenias) peripheral blood should be assessed for clonal lymphocytes.

**Final Response Assessment**Final response assessment will occur two months following completion of treatment with study drug. It is acknowledged that to meet International Workshop on Chronic Lymphocytic Leukemia Guidelines ([iwCLL](http://bloodjournal.hematologylibrary.org/content/111/12/5446.full)) for response in CLL, a response assessment must be performed two months from therapy to document responses including a bone marrow to confirm CR and a CT may be indicated or recommended. Therefore, those patients that clinically appear to be in CR will have a bone marrow biopsy and possibly a CT scan to confirm complete responses at least three months after all treatment.

*[Responses will document surrogate clinical activity and will also be reported consistent with* [*iwCLL 2008 guidelines*](http://www.bloodjournal.org/content/bloodjournal/111/12/5446.full.pdf?sso-checked=true)*. Final Response assessment will be assessed per iwCLL criteria with clinical CRs confirmed by bone marrow biopsy and CT scan should be performed if previously abnormal. The primary efficacy point is response assessed following three treatment cycles.]*

## Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v5.0 for reporting of nonhematologic adverse events and modified criteria for hematologic adverse events. See Section 7.

# Correlative Studies/Special Studies

*Briefly describe all planned correlative studies. For each, indicate if it is mandatory or optional. Explicit instructions for the handling, preserving, and assaying of the specimens should be provided in the biospecimen appendix, and not below. If samples will be shipped to a central laboratory for processing and analysis, responsible parties and contact information should also be provided in the biospecimen appendix, and not below. Refer to Biological Sample Submission study calendar in Appendix 3.*

*A statistical analysis plan of the correlative studies results should be provided in Section 11 Analysis of Secondary Endpoints.*

## *Correlative #1*

## *Correlative #2*

# Statistical Considerations

* A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial and entire trial. [GCP 6.4.6]
* Maintenance of trial treatment randomization codes and procedures for breaking codes. [GCP 6.4.8]
* Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures for specifying: (a) when and how to withdraw subjects from the trial/investigational product treatment; (b) the type and timing of the data to be collected for withdrawn subjects; (c) whether and how subjects are to be replaced; and (d) the follow-up for subjects withdrawn from investigational product treatment/trial treatment. [GCP 6.5.3] (See also Section 4 STUDY ENTRY AND WITHDRAWAL PROCEDURES.)
* Methods and timing for assessing, recording, and analyzing of efficacy parameters. [GCP 6.7.2] (See also Section 4 STUDY ENTRY AND WITHDRAWAL PROCEDURES; Section 9 MEASUREMENT OF EFFECT; STUDY CALENDAR.)
* The methods and timing for assessing, recording, and analyzing safety parameters. [GCP 6.8.2] (See also Section 5 TREATMENT PLAN; Section 7 ADVERSE EVENTS; STUDY CALENDAR; Section 12 DATA AND SAFETY MONITORING PLAN.)
* A description of the statistical methods to be employed, including timing of planned interim analysis(ses). [GCP 6.9.1]
* The number of subjects planned to be enrolled. In multicenter trials, the numbers of enrolled subjects projected for each trial site should be specified. Reasons for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification. [GCP 6.9.2]
* The level of significance to be used. [GCP 6.9.3]
* Criteria for the termination of the trial. [GCP 6.9.4]
* Procedures for accounting for missing, unused, and spurious data. [GCP 6.9.5]
* Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate). [GCP 6.9.6]
* The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects). [GCP 6.9.7]

*Please note that this section should be filled out after consulting your OnCore®  representative.*

## Study Endpoints

*Specify the study design and all study endpoints. State the phase and key design aspects of the study (open label, randomized, blinded, single or multicenter, etc.). Include information on how toxicity will be graded and reported. State that all patients who receive any amount of the study drug will be evaluable for toxicity. Define the dose escalation scheme and MTD definition (or refer to the section where they are defined), accelerated escalation designs with intrapatient dose escalation are encouraged. See example of an* [*accelerated titration design*](http://linus.nci.nih.gov/~brb/Methodologic.htm) *created by NCI’s Biometric Research Branch. If an optimal biologic dose will be determined in place of or in addition to the MTD, define how this will be done, and FDA’s Guidance documents for* [*Dose-Response*](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073115.pdf) *as well as* [*Statistical Principles for Clinical Trials*](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073137.pdf)*.*

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

*For phase 1 study recommendations, please see: Ivy SP, L Siu, E Garrett-Mayer, and L Rubinstein (2010)* [*Approaches to phase I clinical trial design focused on safety, efficiency, and selected patient populations:*](http://clincancerres.aacrjournals.org/content/16/6/1726.abstract) *A report from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. Clin Cancer Res 1(6):1726.*

*For phase 2 study recommendations, please see: Seymour L, SP Ivy, D Sargent, et al. (2010)* [*The design of phase 2 clinical trials testing cancer therapeutics:*](http://clincancerres.aacrjournals.org/content/16/6/1764.abstract) *Consensus recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. Clin Cancer Res 16(6):1764.*

## Study Design

*Provide a detailed statistical design statement.*

## Randomization

* 1. Stratification Factors  
     *Specify any planned patient stratification factors. Indicate whether dose escalation and MTD determination will be done for each stratum individually.*

## Determination of Sample Size and Accrual Rate

## Sample Size and Power Estimate

*Specify the planned sample size and accrual rate (patients per time frame). Add information regarding advance imaging sample size as appropriate. Provide justification for the number of patients to be used in the study. State what the statistical power and sample size considerations are for the proposed study, and which objective they address (should be the primary objective.) State the total sample size, total accrual, expected accrual rate and relevant assumptions. State how these numbers were calculated, including the software used. A reviewer should be able to duplicate the calculations given the information provided.*

## Replacement Policy

## Accrual Estimates

*Provide an estimate of the number of eligible patients yearly. Describe in detail how the estimate was calculated. Include a plan of what will happen if accrual falls short of expectations.*

*If the sample size is justified by power, state the null and alternative hypotheses, the significance level and the power and the method by which it was calculated. Otherwise comment on the expected precision of the estimates to be calculated. If there is substantial uncertainty in the effect size or other aspects of the calculation, provide power for multiple plausible scenarios and explain. Justify the effect size used in the previous subsection. If this is a single-arm (nonrandomized) study, justify the historical control rate. Refer to the section that summarizes the literature on which it is based. List the point estimate, sample size and confidence interval corresponding to each cited study, and describe how you processed those estimates to yield a single number, for example by accounting for population differences and uncertainty. If the sample size is justified by precision only, state the outcomes that constitute success. If the protocol is part of a sequence of trials, state the statistical criteria that will be applied. If this is a pilot study, state what result would convince you to begin a fully powered study.*

## Interim Analyses and Stopping Rules

*If a statistical stopping rule is included, give details to make the rule unambiguous, including when the relevant outcome is to be evaluated, for example:*

*“Response for the purpose of the interim analysis will be evaluated at the end of # cycles.”   
  
The details need to specify how the stopping rule will preserve the significance level coverage of confidence intervals or other relevant aspects of inference.*

## Analyses Plans

*Describe how each objective (particularly the primary objective) will be addressed by a particular data analysis plan. Provide the details of each data analysis plan for each objective — stating what statistical methods will be used, and under which assumptions. Every objective, every study endpoint should have a plan associated with it. Additional details concerning safety and/or pharmacokinetics may be given here as well. Confirm that plan(s) analyze the measurement described in Section 9 and satisfies the Section 2 objectives, referring to those sections as appropriate. Describe any plans for descriptive statistics and exploratory data analysis.*

*All trials must have a named individual who takes responsibility for the biostatistical aspects of the study. The biostatistician’s responsibilities should be defined in this section.*

### **Analysis Population**

*Define the participant subset included in each analysis. Include handling of missing data and nonadherence to protocol.*

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

* + 1. **Secondary Analysis (or Analysis of Secondary Endpoints)**
    2. **Other Analyses/Assessments**

11.11 Evaluation of Safety  
  
Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v5.0.

## 11.12 Study Results

# Data and Safety Monitoring Plan (DSMP)

* The methods and timing for assessing, recording, and analyzing safety parameters. [GCP 6.8.2] (See also Section 5, TREATMENT PLAN; Section 7, ADVERSE EVENTS; STUDY CALENDAR; Section 11, STATISTICAL CONSIDERATIONS.)
* Quality Control and Quality Assurance [GCP 6.11]

**Please refer to the MCWCC DSMC Charter.**

**Data and Safety Management Overview**

The Medical College of Wisconsin (MCW) Data Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with (biannual, monthly) safety and progress reports submitted to the DSMC.

*If applicable add:*

Local, investigator-initiated phase III trials and trials that propose to include **more than 300 participants**will be monitored in a manner and schedule determined by protocol-specific data and safety monitoring boards [DSMB]. Formal DSMBs will consist of clinical investigators, biostatisticians, clinical trial experts, and lay patient advocates independent of investigators involved in the design and conduct of the trial. Following protocol review and monitoring, all DSMB recommendations and reports will be forwarded to the IRB, DSMC and principal investigator.

The DSMP for this study will involve the following entities:

## Study Team

*This section should be included for all studies. The following language should be tailored for a study that involves more than minimal risk. It should be modified as necessary to meet the needs of a particular study.*

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist and the study biostatistician. While subjects are on treatment, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status *(attendees and time periods should be modified so as to make sense within the context of the study).* This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. All meetings including attendance are documented.

## Quality Assurance

The MCWCC Clinical Trials Office provides ongoing quality assurance audits.

## Clinical Trials Office

The MCWCC Clinical Trials Office provides administrative assistance and support to the DSMC.

## DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website ([Data and Safety Monitoring Plan](https://www.mcw.edu/departments/cancer-center/clinical-trials/starting-a-cancer-clinical-trial)).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

* Review the clinical trial for data integrity and safety.
* Review all DSM reports.
* Submit a summary of any recommendations related to study conduct.
* Terminate the study if deemed unsafe for patients.

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study principal investigator twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

# Regulatory Compliance, Ethics and Study Management

* *A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s). [GCP 6.2.5]*
* *Description of ethical considerations relating to the trial. [GCP 6.12]*

## Ethical Standard

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

## Regulatory Compliance

This study will be conducted in compliance with:

* The protocol
* Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

## Prestudy Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MCW IRB.

***If a protocol requiring an IND, add:***

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

## 13.4 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

**Informed Consent Process**

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/‌products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

*For Phase I trials:*

Phase I studies are typically designed to determine safety, but not effectiveness. The phase I consent documents will include approved MCW IRB language found within the IRB-approved template.

*For Phase II and III trials:*

Potential subjects will be told and a statement will be included that this study is designed to determine both safety and effectiveness. The consent forms will include the approved MCW IRB template language.

Consent forms will be IRB-approved and the subject (and legally authorized representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., “Although not required, the subject’s spouse was present during the consenting process and signed as the witness.” Or “Although not required, hospital staff was present for consenting process and signed as a witness.”)

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Patients who require reconsenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB’s policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject’s visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject’s satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject’s study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

## 13.5 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor/sponsor-investigator (*choose one as appropriate*), participating investigators, and any staff, [and the sponsor(s) and their agents] *(include bracketed portion if applicable)*. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor/sponsor-investigator/principal investigator/study chair *(choose one as appropriate)*.

The conditions for maintaining confidentiality of the subjects’ records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject’s data/PHI are stored in the locked Clinical Research Office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the case report forms contain the study identifiers, subject initials, date of birth and date of service.

*Include this information, as appropriate to your study:*

Personal identifiers, such as name and medical record number, will be removed from accompanying lab reports and test results. Any data/PHI that are not stored for the purposes of the study are shredded in the Clinical Trials Office.

After all study queries and analyses are completed, the data/PHI will not be destroyed but will be archived in a secure long-term storage site in order to keep an accurate record of screened and enrolled subjects for the sponsor and potential audit purposes only specific for this study. Data/PHI would not be destroyed until permission is granted by the sponsor to destroy the records.

*If not covered in a separate agreement, the sponsor should ensure the investigators/institutions will allow access to all source data and documents for the purposes of monitoring, audits, IRB review and regulatory inspections. Sample text below:*

The sponsor/sponsor-investigator/principal investigator/study chair *(choose one as appropriate)* will allow access to all source data and documents for the purposes of monitoring, audits, IRB review and regulatory inspections.

The study monitor or other authorized representatives of the sponsor/sponsor-investigator/principal investigator/study chair *(choose one as appropriate)* may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

## 13.6 Protection of Human Subjects

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

**13.6.2 Protection of Privacy**

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient’s medical records, and each patient will receive a copy of the signed document.

13.7 Changes in the ProtocolOnce the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents and reported to the DSMC and IRB per institutional guidelines.

## 13.8 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Onsite Audits

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

# Data Handling and Record Keeping

* *Access to Source Documents/Data: The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents. [GCP 6.10]*
* *Data handling and record keeping. [GCP 6.13]*

*Include instructions for special data handling or record keeping procedures required for maintaining participant confidentiality, any special data securing requirements, and record retention per the sponsor’s requirements in this section. If not contained in another written agreement, include information allowing the sponsor to have access to all trial-related data.*

*Briefly describe steps to be taken to ensure that the data collected are accurate, consistent, complete and reliable. The description should include reference to source documentation, CRFs, instructions for completing forms, data handling procedures and procedures for data monitoring. Details may be provided in another referenced document.*

*Describe responsibilities for data handling and record keeping as they specifically relate to the sponsor, clinical site, laboratory and data coordinating center. Information should include the role in data collection, review of data, trial materials, and reports. Sample text for a multisite* *study involving an IND is given below (modify accordingly to meet the needs of a particular study):*

## Overview

Every effort is made to uphold the integrity of the project, the research, the institution and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss or theft. This project’s data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

## 14.2 Data Management Responsibilities

**14.2.1 Principal Investigator**

The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication and investigational product(s), measurements, exams, evaluations and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the case report forms and the source documents**.**

**14.2.2 Research Coordinator** A research coordinator creates, collects and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol specified time points.

**14.2.3 Research Nurse/Medical Staff**

The research nurse and medical staff document protocol-required care or assessment of the subject’s outcomes, adverse events and compliance to study procedures.

**14.2.4 Biostatistician**

The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

## 14.3 Handling and Documentation of Clinical Supplies

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

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

## 14.4 Source Documents

***Provide a description of the source documents which include all information, original records of clinical findings****, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Sample text below:*

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient’s clinical file. Source documents for the correlative studies are maintained in the laboratory conducting the study.

The source documents for this protocol are as follows:

*Original documents, data and records (e.g., 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 copies, 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).*

All source documents will be written following ALCOA standards:

|  |  |
| --- | --- |
| ALCOA Attribute | Definition |
| Attributable | Clear who has documented the data. |
| Legible | Readable and signatures identifiable. |
| Contemporaneous | Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified. |
| Original | Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document. |
| Accurate | Accurate, consistent and real representation of facts. |
| Enduring | Long-lasting and durable. |
| Available and accessible | Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time. |
| Complete | Complete until that point in time. |
| Consistent | Demonstrate the required attributes consistently. |
| Credible | Based on real and reliable facts. |
| Corroborated | Data should be backed up by evidence. |

## 14.5 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific case report forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The clinical research coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

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

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

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

## 14.6 Study Record Retention

*Specify the length of time for the investigator to maintain the records pertaining to this study.*

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

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

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

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

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

## 14.7 Publishing Data

*Make a brief statement regarding data ownership — who will possess data, and who will publish. For federally funded research, ownership of data involves at least three different entities: the sponsoring institution, the funding agency, and the PI. In many cases, the institution/organization owns the project data, but the PI and the funding agency have "rights" to access and use the data. Usually the PI has physical custody of the data on behalf of the organization. However, these rules vary by institution and the funding source.*

All raw data, data figures, data interpretation, models, and conclusions drawn from this study will be managed by the principal investigator and co-investigators listed in this protocol. The findings from this study are to be presented at relevant conferences/meetings followed by a plan to publish in a respectable peer-reviewed journal. The principal investigators, with assistance from study team members, will be responsible for drafting, overseeing, and finalizing conference abstract submissions, poster and/or oral presentations, or manuscript submission(s) to the journal.

For any manuscript that is to be published in a journal, the role of authors/contributors, the disclosure of financial/non-financial relationships and activities, and the report of perceived conflicts of interest will largely adhere to the recommended guidelines set forth by the International Committee of Medical Journal Editors (ICMJE; [Defining the Role of Authors and Contributors](http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), [Disclosure of Financial and Non-Financial Relationship and Activities and Conflicts of Interest](http://www.icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html)). The PI(s) will coordinate to determine who will be listed as first, senior, and corresponding author(s). Study team members who have made substantial and significant intellectual contributions to the study and its findings will be listed as contributing authors or, in certain circumstances, acknowledged. Funding sources and any conflict of interests, perceived or actual, will be disclosed and stated within the appropriate section of the manuscript at submission.

# References

# Appendix 1. *Performance Status criteria*

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

# Appendix 2. *Prohibited medications*

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

# Appendix 3. *Specimen Collection*

**Sampling and shipping information**[drug name]

* If CTO is processing, follow directions below:
* Draw blood into appropriately mL sized tube (i.e. K2EDTA, NaHeparin, SST)
* Invert the tube gently several times
* Within  min after collection, centrifuge the tube at  C for 15 min at 1500 to 2000g
* Aliquot sample into uniquely labeled 2 ml cryovial and freeze immediately at -70°C or below.
* Coordinate shipping with appropriate lab (on/off campus).

***Sample shipment instructions***

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

A copy of the inventory will be retained at the site in the patient’s binder along with any shipping documents.

All samples will be kept at the temperature specified up to and during the shipment and packed according to IATA shipping regulations.

If shipping samples off campus, shipment will be sent via overnight courier (i.e. FedEx) and shipped Monday through Thursday. Samples will not be shipped on Fridays.

**Tables: THERAPEUTIC PARAMETERS AND BIOLOGICAL SAMPLE SUBMISSIONS**

**Biological Sample Submission**

| **SAMPLE STUDY CALENDAR EXAMPLE No. 1 Biological Sample Submission** | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline**  **(+/- X days)** | **Post Cycle Three**  **(+/- X days)** | **Post Cycle Six (End of Induction)**  **(+/- X days)** | **Every Four (4) Months During First Year of Maintenance**  **(+/- X days)** | **Every Six (6) Months During Second Year of Maintenance**  **(+/- X days)** | **Twelve (12) Months after Completion of Maintenance**  **(+/- X days)** | **Ship to:** |
| MANDATORY for *Central Review* | | | | | | | |
| Diagnostic Tumor Biopsy | X | Any on study biopsy5 | | | | | XYZ (Section X Appendix) |
| Submissions Based on Additional Patient Consent | | | | | | | |
| Peripheral Blood, ACD (yellow top tube)3,6 | X1 | X | X |  |  |  | Clinic X, Y, Z  Laboratory (Section X.X) |
| Peripheral Blood, EDTA (purple top tube)3,5 | X1 | X | X |  |  |  |
| Peripheral Blood, red top tube 3,5 | X1 | X | X |  |  |  |
| Peripheral Blood, EDTA (purple top tube)3,6 | X1 | X | X | X | X | X | Company, Inc.  (Section X.X) |
| Bone Marrow Aspirate, EDTA (purple top tube) 3,6 | X7 |  | X4 |  |  |  |

1. Baseline blood should be collected after randomization, prior to treatment.
2. [Deleted in Addendum #2]
3. Kits are available for the collection and shipment of the blood and bone marrow samples.
4. Patients in CR only.
5. Submit from patients who answer “*Yes*” to “*I agree to provide additional specimens/blood for research*.”
6. Submit from patients who answer “*Yes*” to “*I agree to participate in the laboratory research studies that are being done as part of this clinical trial*.”
7. Patient must sign consent before submission of bone marrow aspirate. If submitting initial bone marrow aspirate to X company prior to patient enrollment to the trial, please call X at X clinic/company (phone number) to obtain an interim patient number. Do not label the tube with any patient identifiers aside from the number given by X. Please use the X submission form when sending the bone marrow to X company. Once the patient has been randomized, please call X with the patient sequence number and enter the information into the sample tracking system.

# Appendix 4. *Lost To Follow-Up Letter (Template)*

Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Dear \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_,

The research study team has been unable to contact you regarding the clinical trial in which you participate.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Sincerely,

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_