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 have questions about the template, you may contact:

|  |  |
| --- | --- |
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# TEMPLATE VERSION HISTORY

| **Version** | **Date** | **Date** |
| --- | --- | --- |
| v2021-02 | 02/11/2021 | * Updated language and tables in *Adverse Events: Definitions, Collection, and Reporting Requirements* section.
 |
| v2021-08 | 08/26/2021 | * Fixed outdated MCW DSMP link in *Data and Safety Monitoring Plan* section.
 |
| v2021-09 | 09/22/2021 | * 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 | 11/03/2021 | * 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 | 11/12/2021 | * 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. |
| v2023-10 | 10/16/2023 | * Updated formatting throughout
* Updated link in introductory paragraph of Section 4.0
* Revised “On Study” definition in Section 4.1
* Revised introductory paragraph of Section 4.6, which now reads as follows:

Eligibility will be evaluated by the study team according to the following criteria. Subjects must meet all inclusion and none of the exclusion criteria to be registered on to the study. Any questions or concerns regarding eligibility should be directed to the PI, Dr. <<*principal investigator name*>> (<<*principal investigator email address*>>). After consent, subjects will receive the designated procedure as prescribed.No waivers of protocol eligibility will be granted.* Revised Adverse Events and Other Reportable Events section to include language defining and how to report protocol deviations to the appropriate regulatory bodies.
 |
| v2024-08 | 08/14/2024 | * Updated formatting throughout.
* Updated hyperlinks throughout.
* Added instructions on how to create a Table of Contents using the Headings function.
* Updated Measurement of Effect section (Section 8.0) describing response criteria using the current NCI CTEP protocol template.
* Revised Section 11.1 to eliminate the choice of biannual or annual progress report submission to the DSMC. The section now states that safety and progress reports will be submitted to the DSMC “periodically.”
* Updated Section 11.3 to indicate that the MCW Cancer Center (MCWCC) Data and Safety Monitoring Committee (DSMC) provides ongoing quality assurance audits.
* Updated Section 11.3 to indicate that the study will be categorized by the MCWCC Scientific Review Committee (SRC) and reviewed internally by the MCWCC DSMC Quality Assurance Staff,
* Added language to Section 13.7 describing trial registration and data reporting requirement to ClinicalTrials.gov.
 |
| v2025-02 | 02/05/2025 | * Added Section 6.2.2, which describes special instructions for recording adverse events.
* Updated the default language in Section 6.2.1 to limit the definition of “all adverse events” that are to be collected per the protocol, which now reads as follows.

*All AEs, including abnormal clinically significant laboratory test results (unless otherwise specified), required to be collected must be graded according to the NCI CTCAE v5.0.** Added language indicating Grade 3 unexpected adverse events must be reported to the MCW Cancer Center (MCWCC) Data and Safety Monitoring Committee (DSMC)
 |

***DELETE TEMPLATE VERSION HISTORY PAGES PRIOR TO SUBMISSION***

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



***PROTOCOL LONG TITLE***

Short Title

***Protocol Short Title***

Principal Investigator

***First Name, Last Name, Credentials***

Clinical Trials.gov Number

NCT***XXXXXXXX***

Version 1.0

*MM*/*DD*/*YYYY*

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.

# **STUDY AND CONTACT INFORMATION**

|  |
| --- |
| Title: *Protocol Long Title* |
| MCW OnCore™ No.: IIT-*XXXXXXXX* | FDA IND No.: *XXXXXX* |
| **MCW Protocol No.:** PRO*XXXXXXXX* |  |
| **Principal Investigator/Study Chair/Coordinating Center/Sponsor-Investigator:** (*Use one as appropriate*)*Investigator Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* | **Co-Investigator:** (*if applicable*)*Investigator Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* |
| **Co-Investigator:** (*if applicable*)*Investigator Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* | **Co-Investigator:** (*if applicable*)*Investigator Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* |
| **Co-Investigator:** (*if applicable*)*Investigator Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* | **Co-Investigator:** (*if applicable*)*Investigator Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* |
| **Biostatistician:** *Biostatistician Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* | **Radiologist:** (*if applicable*)*Radiologist Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* |
| **Pathologist:** (*if applicable*)*Pathologist Name*, *Credentials**Rank/Title* of *Department**Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* | **Pharmacist:** (*if applicable*)*Pharmacist Name*, *Credentials**Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* |
| **Clinical Research Manager:** (*if applicable*)*Research Manager Name*, *Credentials*MCW Cancer Center Clinical Trials OfficeMedical College of Wisconsin9200 W. Wisconsin Ave.Milwaukee, WI 53226Phone: *Phone Number*Email: *Email Address* | **Research Coordinator:** (*if applicable*)*Research Coordinator Name*, *Credentials*MCW Cancer Center Clinical Trials OfficeMedical College of Wisconsin9200 W. Wisconsin Ave.Milwaukee, WI 53226Phone: *Phone Number*Email: *Email Address* |
| **Laboratory Contact:** (*if applicable*)*Lab Contact Name*, *Credentials**Rank/Title* of *Department* (*if applicable*)*Division* (*if applicable*)*Institution**Address**City*, *State* *Zip Code*Phone: *Phone Number*Email: *Email Address* |  |
| **Funding Sponsor:***Identify funding source here* |  |
| **Investigational Agent(s):***List each agent name and indicate if its use is “commercial” or “investigational use” stock. Do not describe the agent(s) here.* |  |

# VERSION HISTORY

|  |  |  |
| --- | --- | --- |
| **Version** | **Date** | **Description of Change(s)** |
| 1.0 | *MM*/*DD*/*YYYY* | Initial version of the protocol |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

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* *In the Table of Contents section, click on the “Table of Contents” button and select “Custom Table of Contents…”*
* *In the Table of Contents window,* set “Show levels” to “2”
* *Click the “OK” button on the window*

**

*To update the Table of Contents, use the following instructions and refer to the image below.*

* *Click on the “References” tab along the top of the page*
* *In the Table of Contents section, click on “Update Table”*
* *Click on either button based on the extent of the revisions made to the protocol*
* *Click the “OK” button on the window*



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# PROTOCOL SUMMARY

*This is meant to be brief. Try to limit the protocol summary to* ***no more than two pages****. Make sure that the items listed on this page match with the corresponding text described in other sections of the protocol.*

|  |  |
| --- | --- |
| **Title** |  |
| **IND Sponsor** |  |
| **Principal Investigator**  |  |
| **Clinical Trial Phase** |  |
| **Study Population** |  |
| **Primary Objective(s)** |  |
| **Secondary Objective(s)** |  |
| **Exploratory Objective(s)** |  |
| **Primary Endpoint(s)** |  |
| **Secondary Endpoint(s)** |  |
| **Exploratory Endpoint(s)** |  |
| **Study Design** |  |
| **Main Eligibility Criteria** | Refer to [Section 4.5](#_Eligibility_Criteria) for the inclusion and exclusion criteria. |
| **Study Agent/Intervention Description** |  |
| **Number of Subjects** |  |
| **Subject Participation Duration** |  |
| **Estimated Time to Complete Enrollment:** |  |

STUDY 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:*

[**Microsoft PowerPoint**](https://www.microsoft.com/en-us/microsoft-365) – Widely known for its ability to create slideshow presentations, PowerPoint can also be used to create flow charts, models, and figures that can be converted into a picture file and easily inserted into this template.

[**Draw.io**](https://www.draw.io/) – A free, online diagram software for making flow charts, process diagrams, organization charts, UML, ER and network diagrams.

[**Microsoft Visio**](https://www.microsoft.com/en-us/microsoft-365/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-and-drop interface.

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

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

# SCHEDULE OF EVENTS

* 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 8 MEASUREMENT OF EFFECT; Section 10 STATISTICAL CONSIDERATIONS.)
* The methods and timing for assessing, recording, and analyzing safety parameters. [6.8.2] (See also Section 5 TREATMENT PLAN; Section 6 ADVERSE EVENTS; Section 10 STATISTICAL CONSIDERATIONS; Section 11 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 and test that 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, and 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. Footnotes should indicate special instructions or notes (e.g., clarification of the procedures, special screening procedures, exceptions). 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 table below is simply a suggestion.*

|  |
| --- |
| *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*. |
| **Procedures and Assessments** | **Screening/Baseline** | **On Treatment** | **End of Treatment** | **Follow-Up** |
| ***Cycle 1*** | ***Cycle 2 and Future Cycles*** |
| **Day-# to -1** | **Day1** | **Day8** | **Day15** | **Day22** | **Day1** | **Day8** | **Day15** | **Day22** |
| Study Window |  | ±# days | ±# days | ±# days | ±# days | ±# days | ±# days | ±# days | ±# days | ±# days | ±# days |
| *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 |
| **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* |  |  |  |  |  |  |  |  |  |  |  |
| *<< 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* |  |  |  |  |  |  |  |  |  |  |  |
| *Urinalysis* |  |  |  |  |  |  |  |  |  |  |  |
| *Pregnancy Test (HCG)* |  |  |  |  |  |  |  |  |  |  |  |
| *<< insert as needed >>* |  |  |  |  |  |  |  |  |  |  |  |
| **IMAGING PROCEDURES** |
| *Imaging (CT or MRI) 9* |  |  |  |  |  |  |  |  |  |  |  |
| *Cardiac Assessment (ECHO, MUGA)* |  |  |  |  |  |  |  |  |  |  |  |
| *ECG/EKG* |  |  |  |  |  |  |  |  |  |  |  |
| *Bone Scan* |  |  |  |  |  |  |  |  |  |  |  |
| *<< insert as needed >>* |  |  |  |  |  |  |  |  |  |  |  |
| **RESEARCH CORRELATIVE PROCEDURES** |
| *Specimen Collection or Optional Specimen Banking* |  |  |  |  |  |  |  |  |  |  |  |
| *Questionnaire* |  |  |  |  |  |  |  |  |  |  |  |
| *<< insert as needed >>* |  |  |  |  |  |  |  |  |  |  |  |

**Footnotes**

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).*
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 a study-appropriate term)

*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 10 of this document. This section should connect the disease background with the study drug(s) 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 (replace header with agent name to be tested)

*This is intended to be a brief summary of Section 7, 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

## Other Agents (replace header with other investigational agents)

### Preclinical Data

### Clinical Data

## Rationale

## Known **Risks** and Potential Benefits

## 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).

# 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. [GCP 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 Section 3, 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 Objective(s)

*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).*

*State the primary protocol objective. It should have a corresponding endpoint described in Sections 3 and 10. For example, a typical primary objective for a phase 1 trial can be:*

* + - 1. 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 Objective(s)

*The secondary objective(s) are goals that will provide further information on the use of the intervention.*

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

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

## Primary Endpoint(s)

The clinical trial **primary endpoint** is the endpoint for which the trial is powered. This information should be identical to Section 11.

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.*

*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 or randomized.”*

*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.*

## Exploratory Endpoint(s)

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

***ALTERNATIVE FORMATTING OF SECTION 2.0***

*In lieu of listing objectives and endpoints under separate headings (Sections 2.1 through 2.5), they can be presented as a table, as shown in the example below. Presenting the objectives and endpoints as a table better illustrates how each objective is aligned with its corresponding endpoint measurement. If presenting the objectives and endpoints as a table, remove Sections 2.1 through 2.5 from the document.*

**Table 2-1. Study Objectives and Endpoints**

|  |  |
| --- | --- |
| **Primary Objective(s)** | **Primary Endpoint(s)** |
| 1. To assess disease-free survival (DFS) in all subjects at six months.
 | * + - 1. Disease-free survival at six months is defined as the time from study therapy initiation until disease recurrence based on CT, MRI, or PET imaging.
 |
| 1. To assess the safety and toxicity of the study intervention
 | 1. The incidence of clinically relevant Grade 3 and 4 AEs and SAEs that are at least possibly related to the study therapy per investigator assessment.
 |
| **Secondary Objective(s)** | **Secondary Endpoint(s)** |
| 1. To assess overall survival (OS) in all subjects treated with the study intervention.
 | 1. Overall survival is defined as the time from study therapy initiation until death from any cause.
 |
| 1. To assess disease-free survival (DFS) in all subjects treated with the study intervention.
 | 1. Disease-free survival is defined as the time from study therapy initiation until disease recurrence or death from any cause.
 |
| **Exploratory Objective(s)** | **Exploratory Endpoint(s)** |
| 1. *To correlate the levels of proteins involved in apoptosis with therapy response.*
 | 1. Determine the expression of BCL2, BCLXL, MCL1, BAX, and BAK and correlate with treatment response.
 |

# STUDY DESIGN

PURPOSE: The study design presents how and when the objectives will be measured.

* 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. [GCP 6.4.2] (See also the SCHEMA Section.)
* A description of the measures taken to minimize/avoid bias, including: (a) randomization; (b) blinding. [GCP 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 *XX* 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 *XX* months from the time the study opens to accrual.

# SUBJECT PARTICIPATION, DISCONTINUATION, AND WITHDRAWAL

Medical College of Wisconsin (MCW) investigators and study personnel must follow all MCW Institutional Review Board (IRB) requirements and policies regarding subject participation, found here:

<https://www.mcw.edu/departments/human-research-protection-program/researchers/irb-policies-and-procedures>

## 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: date the subject is eligible or, if not the same day, deemed to be on study.
* 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 trial participation with or without consent, but are not subsequently assigned to the study intervention or enrolled in the study. The MCW Cancer Center (MCWCC) Clinical Trials Office (CTO) will follow its Standard Operating Procedures (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](#_STUDY_CALENDAR) for screening and registration timeline.

*Specific screening requirements should be noted here or as a footnote in the Study Calendar.*

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. Patients who previously failed screening *may/may not* be rescreened.

## Eligibility Criteria

Eligibility will be evaluated by the study team according to the following criteria. Subjects must meet all inclusion and none of the exclusion criteria to be registered on to the study. Any questions or concerns regarding eligibility should be directed to the PI, Dr. <<*principal investigator name*>> (<<*principal investigator email address*>>). After consent, subjects will receive the designated procedure as prescribed.

No waivers of protocol eligibility will be granted.

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) or 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 10 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

A potential study subject who meets all of the following inclusion criteria is eligible to participate in the study.

*Criteria that 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. Age >18 years
2. *State any age and/or gender/race-ethnic restrictions.*
3. 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)]

1. *Provide appropriate criteria for the lesion measurement in this patient population. Lesions are either measurable or nonmeasurable, using the criteria provided in Section 8 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 8 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).*

1. *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).*
2. *State allowable type and amount of prior therapy.*
3. State any life expectancy restrictions.
4. *State whether ECOG or Karnofsky Performance Status will be employed (see Appendix 1 Performed Status Criteria).*
5. State requirements for organ and marrow function, examples provided below:

**Table 4-1. Organ and Marrow Function**

|  |
| --- |
| **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” |

1. 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.*

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

### 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.*

1. *State restrictions regarding use of other investigational drugs.*
2. *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.*
3. State requirements regarding history of allergic reactions attributed to compounds of similar chemical or biologic composition to investigational drug or device.
4. 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.*

1. 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:* 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.*

1. *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.]*.

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

|  |
| --- |
| *“I have reviewed all inclusion/exclusion criteria and confirm the subject is eligible.”* |
|  |
| **Enrolling Investigator Name (Print)** |
|  | / / |
| **Enrolling Investigator Signature** | **Date** |

## Discontinuation of Study Treatment, Withdrawal, and Compliance

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 that render them unacceptable for further treatment in the investigator’s judgment.
* Intercurrent illness that prevents further treatment administration.
* The 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.

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.

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.>>

## 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.

## 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.

## End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study, including the last visit or the last scheduled procedure shown in the [Schedule of Events](#_STUDY_CALENDAR) table or has been discontinued.

## 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 5 TREATMENT PLAN; Section 6 ADVERSE EVENTS.)
* The methods and timing for assessing, recording, and analyzing safety parameters. [GCP 6.8.2] (See also Section 6 ADVERSE EVENTS; Section STUDY CALENDAR; Section 10 STATISTICAL CONSIDERATIONS; Section 11 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.

Patients must meet the eligibility criteria on Day 1 to be treated. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

*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.*

**Table 5-1. Study Treatment Administration Overview**

| **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. *List table footnotes here*.

## 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.*

**Table 5-2. *Study Drug 1* Dose Escalation Levels.**

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

Footnotes. *State exact dose in units (mg/m2, mcg/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.

**Table 5-3. *Study Drug 1* Dose Escalation Rules.**

| **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.*

### Dose-Limiting Toxicity

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

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

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

*[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.*

### 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.*

### Dietary Restrictions

### 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.*

## Dosing Delays and 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 6 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 examples below and choose a format that best fits the need of the study.*

**Table 5-4. *Study Agent 2* Dose Levels**

| **Dose Level** | **Dose of Study Drug** |
| --- | --- |
| -1 |  |
| 1 |  |
| 2 |  |
| 3 |  |

Footnotes. *List footnotes here.*

**Table 5-5. *Study Agent 3* Dose Levels**

| **Dose Level** | **Dose of Study Drug** |
| --- | --- |
| -1 |  |
| 1 |  |
| 2 |  |
| 3 |  |

Footnotes. *List footnotes here.*

**Table 5-6. *Study Agent 2 and Study Agent 3* 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 Study Agent 2 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, Study Agent 2 may be reinitiated with 1 dose level reduction and upon recurrence of same toxicity  lower Study Agent 2  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 X-Y***
* *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 X-Y****.*
* *Upon recovery, reduce  Study Agent 2 first and then Study Agent 3 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 Study Agent 2 or Study Agent 3 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 Study Agent 3 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 CTCAE v5.0.

*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.*

**Table 5-7. Dose Modifications and Dosing Delays for Specific Adverse Events**

|  |  |  |
| --- | --- | --- |
| **Grade of Event** | **Management for *Study Agent 2*** | **Management for *Study Agent 3*** |
| ***Nausea*** |
| *≤ 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* |
| ***Vomiting*** |
| *≤ 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* |
| ***Diarrhea*** |
| *≤ 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* |
| ***Neutropenia*** |
| *≤ 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 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

**Table 5-7. Other Toxicities**

|  |  |
| --- | --- |
| Cardiovascular toxicity | A major potential toxicity with << study drug >> is << AE >>, which will also be graded on the basis of the NCI CTCAE 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.**

## Monitoring Subject Compliance (if applicable)

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified co-investigator(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.

# ADVERSE EVENTS AND OTHER REPORTABLE INCIDENTS

## Definitions

### Adverse Event (AE)

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

This study will utilize the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0), located on the CTEP website:

<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.** 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 that 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.** 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 any abnormal clinically significant 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, including abnormal clinically significant laboratory test results (unless otherwise specified), required to be collected must be graded according to the NCI CTCAE v5.0. 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 6.2.2*** and ***Table 6-1*** to identify the adverse events that need to be reported.

### Other Considerations for Recording Adverse Events

#### Hospitalizations for Medical or Surgical Procedures

Any AE that results in inpatient hospitalization ≥ 24 hours or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

* Inpatient hospitalization ≥ 24 hours or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions;
* Inpatient hospitalization ≥ 24 hours or prolonged hospitalization required to allow efficacy measurement for the study; or
* Inpatient hospitalization ≥ 24 hours or prolonged hospitalization for scheduled therapy of the target disease of the study.

#### Adverse Events of Special Interest (AESIs) *Note: this section is optional depending on the sponsor/funder’s AE reporting needs. If AESIs are not being collected and reported, remove this section.*

AESIs are a subset of events to monitor of scientific and medical concerns specific to the product, for which ongoing monitoring and rapid communication by the investigator to the sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., regulatory authorities) may also be warranted.

Adverse events of special interest for this study include the following:

* *List AESIs specific to the study agent here*

### Reporting of Adverse Events and Serious Adverse Events

Please refer to ***Table 6-1*** 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™.

**Table 6-1. Adverse Events and Serious Adverse Events Reporting Requirements1**

|  |  |  |
| --- | --- | --- |
| **Attribution** | **SAEs** | **AEs** |
| **Grade 1, 2 & 3** | **Grade 4 and 5** | **Grade 3** | **Grade 4**  |
| **Expected** | **Unexpected** | **Expected** | **Unexpected** | **Expected** | **Unexpected** | **Expected** | **Unexpected** |
| **UnrelatedUnlikely** | **DSMC- Routine Review2****Sponsor6** | **DSMC- Routine Review2** | **DSMC3-Within 5 calendar days****Sponsor6** | **DSMC3-Within 5 calendar days** | **DSMC- Routine Review2** | **DSMC3-Within 5 calendar days** | **DSMC-****Heme:Routine review2,4****Non-Heme:Within 5 calendar days3** | **DSMC3-Within 5 calendar days** |
| **PossibleProbableDefinite** | **DSMC3- Within 5 calendar days****FDA5****Sponsor6** | **DSMC3- Within 5 calendar days****FDA5****Sponsor6** |

**Footnotes.**

1. Adverse event reporting to the IRB will follow the MCW Human Research Protections Program SOP on requirements for reporting to the IRB, which can be found on the [MCW IRB Policies and Procedures](https://www.mcw.edu/departments/human-research-protection-program/researchers/irb-policies-and-procedures) website.
2. The DSMC will review events entered in OnCore™ at the time of scheduled monitoring.
3. For 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™.
4. Expected hematological Grade 4 adverse events will be routine reported.
5. Fatal 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 6.2.3.1* for detailed reporting instructions.
6. If sponsor/drug manufacturer windows apply, add these to the table as well and include this footnote: See *Section 6.2.3.2* 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:
<https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting>

#### 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, e.g., fax number, email, etc.*

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

The investigator and their 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 [MCW Human Research Protection Program](https://www.mcw.edu/departments/human-research-protection-program/researchers/irb-policies-and-procedures) website.

## Subject Complaints

If anyone on the study staff receives a complaint, 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 their 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.

## Protocol Deviations

### Definitions

* **Protocol Deviation.** A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator’s control and that has not been approved by the IRB.
* **Significant Protocol Deviation.** Significant protocol deviations are those that increase the risk to participants or others, decrease potential benefits of the project, undermine the scientific integrity of the project, or occur more than once.
* **Planned Protocol Deviation.** Planned protocol deviations are any temporary protocol deviation acknowledged by the IRB prior to its initiation. Any permanent change to the protocol constitutes an amendment that must be submitted to the IRB for approval prior to initiation.

### Reporting Protocol Deviations

Any deviation from the protocol must be fully documented in the source documents. A summary of all protocol deviations must be reported to the DSMC at the time of scheduled monitoring. Per the most recent MCW Office of Research SOP, the following events meet the MCW IRB expedited reporting criteria; any other deviation is to be reported in a timely manner.

* Significant Protocol Deviations. Examples include but are not limited to the following:
	+ Any departure from the protocol (deviation or violation) where subjects or others were harmed or might be at increased risk of harm.
	+ Any departure from the protocol compromises the integrity of the research data.
	+ Any change made to the research without prior IRB approval in order to eliminate apparent immediate harm.
* Planned Protocol Deviations. Planned protocol deviations that increase the risk to participants or others, decrease the potential benefits of the project, or undermine the scientific integrity of the project are considered events that meet MCW’s prompt reporting criteria. Examples include but are not limited to the following:
	+ Enrolling a subject who does not meet the eligibility criteria.
	+ Not performing a specific screening procedure for a patient as indicated in the protocol.

# 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 current investigator’s brochure, pharmaceutical data sheet, 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

*If possible, denote the drug’s classification (e.g., monoclonal antibody, alkylating agent, tyrosine kinase inhibitor)*.

#### Mechanism of Action

*Briefly describe how the drug produces its effect on the system.*

#### Metabolism

*If possible, briefly describe how the drug is chemically altered to create compounds that can be more easily excreted from the body.*

#### Contraindications

*Indicate symptoms or conditions that serve as a reason for a patient to not take the drug due to the harm that it could cause.*

#### Side Effects

Complete and updated adverse event information is available in the Investigational Brochure and/or product package insert. *[is an IB and/or package insert are available; alternatively, a brief description of the side effects can be described in this section]*

### Solution Preparation

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

### Administration

*Briefly explain how the drug is to be administered to the patient (e.g., intravenous infusion, subcutaneously, orally).*

### 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

*If applicable, describe special instructions a nurse should take when administering the drug to the patient (premedication assessments, side effects that should be monitored, etc.)*

### 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 the pharmaceutical company.

### 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.*

# MEASUREMENT OF EFFECT (OR REPORTING AND DOCUMENTING RESULTS)

* 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 10 STATISTICAL CONSIDERATIONS.)

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

*For phase 1 protocols only:* Although the clinical benefit of [this/these] drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every *[# of weeks]* weeks. In addition to a baseline scan, confirmatory scans will also be obtained *[# of weeks]* weeks following initial documentation of an objective response.

*Please use either Section 8.1 or Section 8.2 based on study design. Please note that for studies using immunotherapy, Section 8.2 is recommended as it includes both RECIST version 1.1 and iRECIST criteria.*

## Antitumor Effect – Solid Tumors

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

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

### Definitions

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

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

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

### Disease Parameters

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

Non-Target Lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.*, for body scans).

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

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

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

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

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

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

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

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

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

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

### Response Criteria

#### Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

#### Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

#### Evaluation of Best Overall Response

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

**Table 8-1. Patients with Measurable Disease (*i.e.*, Target Disease)**

| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Overall Response when Confirmation is Required\*** |
| --- | --- | --- | --- | --- |
| CR | CR | No | CR | ≥4 wks. Confirmation\*\* |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. Confirmation\*\* |
| CR | Not evaluated | No | PR |
| PR | Non-CR/Non-PD/not evaluated | No | PR |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥4 wks. from baseline\*\* |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD\*\*\* | Yes or No | PD |
| Any | Any | Yes | PD |

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

\*\* Only for non-randomized trials with response as primary endpoint.

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

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

**Table 8-2. Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)**

| **Non-Target Lesions** | **New Lesions** | **Overall Response** |
| --- | --- | --- |
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD\* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

\* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

### Duration of Response

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

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

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

### Progression-Free Survival

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

### Response Review

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

## Antitumor Effect – Immune-Related RECIST (iRECIST) Criteria

### Definitions

Evaluable for Adverse Events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

Evaluable for Response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (RECIST version 1.1) proposed by the RECIST committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

### RECIST 1.1 Response and Evaluation Endpoints

Measurable Disease. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest X-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions are considered non­measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Target Lesions. When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-Target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent."

### Response Criteria

All patients will have their best response from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): Disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [*Eur J Ca* 45:228-247, 2009]) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): At least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

**Table 8-3. Integration of Target, Non-Target, and New Lesions in Response Assessment**

| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Response for This Category Also Requires** |
| --- | --- | --- | --- | --- |
| **Target lesions ± non target lesions** |
| CR | CR | No | CR | Normalization of tumor markers, tumor nodes <10 mm |
| CR | Non-CR/non-PD | No | PR | Normalization of tumor markers, tumor nodes <10 mm |
| CR | Not all evaluated | No | PR |   |
| PR | Non-PD/not all evaluated | No | PR |   |
| SD | Non-PD/not all evaluated | No | SD | Documented at least once ≥4 weeks from baseline |
| Not all evaluated | Non-PD | No | NE |   |
| PD | Any | Any | PD |   |
| Any | PD | Any | PD |   |
| Any | Any | Yes | PD |   |
| **Non target lesions ONLY** |
| No Target | CR | No | CR | Normalization of tumor markers, tumor nodes <10 mm |
| No Target | Non-CR/non-PD | No | Non-CR/ non-PD |   |
| No Target | Not all evaluated | No | NE |   |
| No Target | Unequivocal PD | Any | PD |   |
| No Target | Any | Yes\* | PD |   |

\* Investigators should record all new lesions. If the new lesion is felt to be equivocal, treatment may be continued pending further assessments.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

### iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming progression: Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks, after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

* Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease, or new lesions.
	+ Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum.
	+ Continued unequivocal progression in non-target disease with an increase in tumor burden.
	+ Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
* RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD (*Lancet Oncol* 18:e143-e152, 2017 - Table 2).

New lesions: New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis [or 15 mm in short axis for nodal lesions]), and recorded as New Lesions - Target (NLT) and New Lesion - Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

**Table 8-4. Time-point (TP) iResponse**

| **Target Lesions\*** | **Non-Target Lesions\*** | **New Lesions\*** | **Time Point Response** |
| --- | --- | --- | --- |
| **No prior iUPD\*\*** | **Prior iUPD\*\*, \*\*\*** |
| iCR | iCR | No | iCR | iCR |
| iCR | Non-iCR/Non- iUPD | No | iPR | iPR |
| iPR | Non-iCR/Non- iUPD | No | iPR | iPR |
| iSD | Non-iCR/Non- iUPD | No | iSD | iSD |
| iUPD with no change OR decrease from last TP | iUPD with no change OR decrease from last TP | Yes | NA | NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD. |
| iSD | iUPD | No | iUPD | Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD). |
| iUPD | Non-iCR/Non-iUPD | No | iUPD | Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5 mm, otherwise remains iUPD. |
| iUPD | iUPD | No | iUPD | Remains iUPD unless iCPD confirmed based on further increase in: |
| * previously identified T lesion iUPD SOM ≥5 mm and/or
 |
| * NT lesion iUPD (prior assessment - need not be unequivocal PD)
 |
| iUPD | iUPD | Yes | iUPD | Remains iUPD unless iCPD confirmed based on further increase in: |
| * previously identified T lesion iUPD ≥5 mm and/or
 |
| * previously identified NT lesion iUPD (need not be unequivocal) and/or
 |
| * size or number of new lesions previously identified
 |
| Non-iUPD/PD | Non-iUPD/PD | Yes | iUPD | Remains iUPD unless iCPD confirmed based on increase in size or number of new lesions previously identified. |

\* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR, and SD would be the same.

\*\* in any lesion category.

\*\*\* previously identified in assessment immediately prior to this TP.

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

**Table 8-5. iRECIST Best Overall Response (iBOR)**

| **TPR 1** | **TPR 2** | **TPR 3** | **TPR 4** | **TPR 5** | **iBOR** |
| --- | --- | --- | --- | --- | --- |
| iCR | iCR, iPR, iUPD, NE | iCR, iPR, iUPD, NE | iUPD | iCPD | iCR |
| iUPD | iPR, iSD, NE | iCR | iCR, iPR, iSD, iUPD, NE | iCR, iPR, iSD, iUPD, iCPD, NE | iCR |
| iUPD | iPR | iPR, iSD, iUPD, NE | iPR, iSD, iUPD, NE, iCPD | iPR, iSD, iUPD, NE, iCPD | iPR |
| iUPD | iSD, NE | PR | iPR, iSD, iUPD, NE | iPR, iSD, iUPD, iCPD, NE | iPR |
| iUPD | iSD | iSD, iUPD, NE | iSD, iUPD, iCPD, NE | iSD, iUPD, ICPD, NE | iSD |
| iUPD | iCPD | Anything | Anything | Anything | iCPD |
| iUPD | iUPD | iCPD | Anything | Anything | iCPD |
| iUPD | NE | NE | NE | NE | iUPD |

Table assumes a randomized study where confirmation of CR or PR is not required.

* NE = not evaluable that cycle.
* Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
* For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

### Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

### Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.*, 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion."

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (*e.g.*, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.*, for body scans). Other specialized imaging or other techniques may also be appropriate for individual case (*Eur J Ca* 45:228-247, 2009). For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

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

Tumor Markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (*e.g.*, with certain taxane compounds or angiogenesis inhibitors), 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 advised to differentiate between response or SD and PD.

## Antitumor Effect – Hematologic Tumors

*Please provide appropriate criteria for evaluation of response and methods of measurement. Add subsections as needed.*

## Other Response Parameters

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

## 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 for reporting of nonhematologic adverse events and modified criteria for hematologic adverse events. Refer to [Section 6.0](#_ADVERSE_EVENTS_AND) for additional details on adverse events definition, collection, and reporting.

# 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 the Analysis Plan (Section 10.7).*

## 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 8 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 6 ADVERSE EVENTS; STUDY CALENDAR; Section 11 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 the study biostatistician and 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

*Describe the randomization procedures if the study is randomly assigning patients onto a specific study arm.*

## 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

*Describe whether study participants who withdraw from the study will or will not be replaced.*

Participants will/will not be replaced if they withdraw from the study before initiating study therapy.

### 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.*

## Analysis 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 8 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 the* [*Study and Contact Information*](#_STUDY_AND_CONTACT) *page.*

### Analysis Population

*Define the participant subset included in each analysis (the safety population, the efficacy population, etc.).*

### Primary Endpoint Analysis

*Describe the procedures for analyzing the primary endpoint(s). For single-arm trials, indicate, reference, and justify the comparison value for each hypothesis of interest.*

### Secondary Endpoint Analysis

*Describe the procedures for analyzing the secondary endpoint(s).*

### Exploratory Endpoint Analysis

*Describe the procedures for analyzing exploratory endpoint(s).*

## **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.

## Missing Data

*Describe procedures for handling missing data.*

# 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 6, ADVERSE EVENTS; STUDY CALENDAR; Section 10, STATISTICAL CONSIDERATIONS.)
* Quality Control and Quality Assurance [GCP 6.11]

***Please refer to the most recent version of 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 periodic 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 the 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 DSMC provides ongoing quality assurance audits.

This study will be categorized by the MCW Cancer Center (MCWCC) Scientific Review Committee (SRC) and reviewed internally by the MCWCC DSMC Quality Assurance Staff according to the MCWCC [Data and Safety Monitoring Plan](https://cancer.mcw.edu/researchers-and-clinicians/clinical-research/clinical-trial-resources).

## 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 related to the MCWCC Data and Safety Monitoring Plan can be found at the MCWCC [website](https://cancer.mcw.edu/researchers-and-clinicians/clinical-research/clinical-trial-resources).

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 requires 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.

## 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 CFR 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.

## 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.

## Protection of Human Subjects

### 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.

### 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.

## Changes in the Protocol

Once 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.

## 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.

## Data Management Responsibilities

### 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**.**

### Research Coordinator

The research coordinator creates, collects, and organizes clinical trial documentation. They ensure that source documentation and data abstraction and entry are being done at protocol-specified time points.

### 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.

### Biostatistician

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

## 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.

## 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, as shown in **Table 13-1**.

**Table 13-1. 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. |

## 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.

## 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.

## 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 and meetings, followed by a plan to publish them in a respectable peer-reviewed journal. The principal investigator, with assistance from study team members, will be responsible for drafting, overseeing, and finalizing conference abstract submissions, 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.

In accordance with the MCW Human Research Protection Program and Federal regulations FDAAA 801 and 42 CFR Part 11 (per the Final Rule, effective 1/18/2017), information about and results collected from this study will be registered on ClinicalTrials.gov, the clinical trial registry and results data bank operated by the National Library of Medicine (NLM) of the National Institutes of Health (NIH). All informed consent documents will include a specific statement relating to the posting of study information in ClinicalTrials.gov.

# REFERENCES

# APPENDIX 1. Performance Status criteria

|  |  |
| --- | --- |
| **ECOG Performance Status Scale** | **Karnofsky Performance Scale** |
| Grade | Descriptions | Percent | Description |
| 0 | Normal activityFully 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 ambulatoryRestricted 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 timeAmbulatory and capable of all self-care, but unable to carry out any work activitiesUp 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 timeCapable 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 indicatedDeath not imminent |
| 4 | 100% bedriddenCompletely disabledCannot carry on any self-careTotally confined to bed or chair | 20 | Very sick, hospitalization indicatedDeath 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, ZLaboratory (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

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

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

The research study team has been unable to contact you regarding the clinical trial, *Enter Long Title Here*, in which you participated in.

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

Please contact us at

Sincerely,