\*\*\*DELETE THIS PAGE FROM FINAL VERSION\*\*\*

**Protocol Template Instructions**

This template has been created to assist in the development of an interventional *investigator-initiated trial (IIT) protocol*. It is not mandatory that you follow the exact order presented in this template (although this is the preferred format for studies that will utilize services of the Clinical Trials Office). However, all the information contained in this template must be present, in some format, in your final protocol.

**The sections in BLACK are standard/required language for studies under the purview of the Robert H. Lurie Comprehensive Cancer Center and should be included in your protocol and/or revised as needed to reflect the specifics of your trial. In some cases, alternate language choices are included and may be more appropriate.**

Please note that a *Letter of Intent (LOI)* must be submitted and endorsed by the appropriate Disease Team for all Northwestern University interventional investigator-initiated trials prior to full protocol submission. Internal Medical Writers are available to assist with protocol development. After Disease Team Endorsement of your concept, you will be contacted by a Medical Writer for assistance in developing your protocol. Assistance is highly encouraged for consistency and compliance.

**The sections in BLUE provide examples and/or instructions, and details should be modified to fit your specific trial. You may RENAME sections (if appropriate) and/or DELETE any sections that do not apply. The final protocol document should not contain any BLUE text.**

Study Title

*Title should include study phase, design descriptors (e.g., randomized, double-blind, placebo-controlled, multi-center, etc.), the intervention(s), the target population (disease(s) or condition(s), stage, if appropriate, and the setting (e.g. front-line, adjuvant, etc.). Acronyms should be spelled out.*

**Principal Investigator:** Name/Credentials *(One person only - may not be a resident/fellow)*

Institution/Department or Division

Address

City, State, Zip

Phone: [Here]

Fax: [Here]

Email: [Here]

**Sub-Investigator(s):** *For local sub-Is include:*

Name

Department/Division *(may group individuals together from same)*

*For external sub-Is include (one per site):*

Name/Credentials

Institution

Address

City, State, Zip

Phone: [Here]

Fax: [Here]

Email: [Here]

**Biostatistician:** Name

Email: [Here]

*(May include other contact info if biostatistician is external)*

*Complete the following request for a statistician to be assigned:*

<https://redcap.nubic.northwestern.edu/redcap/surveys/?s=7YAAR3YFHJ>

**Study Intervention(s):** *Generic study drug name, followed by marketed name*

**IND Number:** *If IND* ***is required****, list “*pending*” or “*TBD*” until IND Number is available.*

*If IND is* ***not required****, list “*Study Exempt from IND Requirements per 21 CFR 312.2(b)*”. This should be established prior to SIM.*

**IND Holder:** *If IND is* ***required****, list IND Holder (likely PI).*

*If IND is* ***not required****, list “*N/A*”*

*Prior to the Study Implementation Meeting (SIM), you will determine whether an IND needs to be filed based on established regulatory requirements. For Device Trials, IND text should be replaced with IDE.*

**Funding Source**: *List support (funding or investigational agent) from Industry or other sources (provide grant number, if applicable.)*

**Version Date:** MM.DD.YYYY

**Coordinating Center:** Clinical Trials Office

Robert H. Lurie Comprehensive Cancer Center

Northwestern University

676 N. St. Clair, Suite 1200

Chicago, IL 60611

<https://www.cancer.northwestern.edu/research/clinical-trials-office/index.html>

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**LIST OF ABBREVIATIONS**

*It may be helpful to include a list of frequently-used abbreviations. Some examples commonly used in oncology research include (please delete those that are N/A):*

|  |  |
| --- | --- |
| ADC | Antibody-drug Conjugate |
| AE | Adverse Event |
| ALT/SGPT | Alanine Aminotransferase/ Serum Glutamic Pyruvic Transaminase |
| ALC | Absolute Lymphocyte Count |
| ANC | Absolute Neutrophil Count |
| AST/SGOT | Aspartate Aminotransferase/ Serum Glutamic Oxaloacetic Transaminase |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CHF | Congestive Heart Failure |
| CK | Creatinine Kinase |
| CMP | Comprehensive Metabolic Panel |
| CNS | Central Nervous System |
| CR | Complete Response |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTEP-AERS | Cancer Therapy Evaluation Program Adverse Event Reporting System |
| CTO | Clinical Trials Office |
| DLT | Dose Limiting Toxicity |
| DOR | Duration of Response |
| DSMC | Data and Safety Monitoring Committee |
| DSMP | Data and Safety Monitoring Plan |
| ECG | Electrocardiogram |
| ECI | Events of Clinical Interest |
| ECOG | Eastern Cooperative Oncology Group |
| FDA | Food and Drug Administration |
| FDG | flurodeoxyglucose |
| FOCBP | Female of Child-bearing Potential |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| H&PE | History & Physical Exam |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| ICH | International Conference on Harmonisation |
| IHC | Immunohistochemistry |
| INR | International Normalized Ratio |
| irAE | Immune-related Adverse Event |
| IRB | Institutional Review Board |
| IQR | Interquartile Range |
| IV (or iv) | Intravenously |
| KPS | Karnofsky Performance Status |
| LDi | Longest Diameter of a lesion |
| LLN | Lower Limit of Normal |
| mAb | Monoclonal Antibody |
| MRI | Magnetic Resonance Imaging |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| OR | Objective Response |
| ORR | Overall Response Rate or Objective Response Rate |
| OS | Overall Survival |
| PBMCs | Peripheral Blood Mononuclear Cells |
| PD | Progressive Disease |
| PET | Positron Emission Tomography |
| PFS | Progression Free Survival |
| PO (or p.o.) | Per os/by mouth/orally |
| PPD | Perpendicular Diameter of a lesion |
| PR | Partial Response |
| PT | Prothrombin Time |
| aPTT | Activated Partial Thromboplastin Time |
| RANO | Response Assessment in Neuro-Oncology |
| iRANO | Immune Response Assessment in Neuro-Oncology |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| iRECIST | Immune Response Evaluation Criteria in Solid Tumors |
| irRECIST | Immune-Related Response Evaluation Criteria in Solid Tumors |
| RNI | Reportable New Information |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| SDi | Shortest Diameter of a lesion |
| TTP | Time To Progression |
| ULN | Upper Limit of Normal |
| WBC | White Blood Cells |

**STUDY SCHEMA**

*The schema should be a diagram or pictorial representation of your study design and general treatment plan. For example:*

Stage I/II Cancer A

Randomize

Arm B

Drug 1 at dose X

IV Day 1 of each cycle

1 cycle = XX days

+

Placebo

PO daily

Arm A

Drug 1 at dose X

IV Day 1 of each cycle

1 cycle = XX days

+

Drug 2 at dose X

PO daily

Response Assessment after X cycles

Once off Treatment

Continue Survival Follow Up every 3 months for X years

Replace placebo with Drug 2 & Re-assess after X Cycles

CR/PR/SD

Continue Drug 1 until PD

PD

Proceed to surgery off study

CR/PR/SD

Continue treatment until PD

**STUDY SUMMARY**

|  |  |
| --- | --- |
| **Title** | Full title of protocol |
| **Version** | Include date & amendment number. |
| **Study Design** | Study phase & design attributes such as single blind, double blind or open label; randomized, placebo or active placebo control; cross-over design, Simon two-stage, etc. |
| **Study Center(s)** | If multi-center, list all projected centers to be involved & indicate who the lead site will be. Participating sites should be established at time of endorsement, at disease team meeting, if possible, and no later than the SIM. If sites are not known, should be listed as “single-center” until sites are identified. |
| **Objectives** | At a minimum list all primary & secondary objectives (can refer to body of protocol for any exploratory objectives). |
| **Sample Size** | Number of patients projected for the entire study (may specify by phase if phase I/II trial). |
| **Diagnosis & Key Eligibility Criteria** | Note the main clinical disease state under study and some of the significant inclusion or exclusion criteria (do not list all criteria here) |
| **Treatment Plan** | Brief overview of treatment plan including study intervention(s) and dose/route/regimen or other description of therapy (for non-drug or biologic). Also state overall treatment/intervention timeframe. *NOTE: If name-brand agent is used in the study, may reference the marketed name in background or drug info section, but should use generic name throughout majority of the protocol.* |
| **Statistical Methodology** | A very brief description of the main elements of the statistical methodology to be used in the study (sample size and power calculation, brief discussion of primary endpoint analysis). |

# Introduction – BACKGROUND & RATIONALE

## Disease Background

***Please provide disease background information particularly relevant to your study, such as incidence, prognosis or current data corresponding to planned endpoints; be specific about the population being studied (e.g. relapsed/refractory disease or previously untreated or those possessing a particular genetic marker, etc.). Questions to be addressed may include the current standard of care and any relevant treatment issues or controversies. Please justify why an investigational therapy or approach is warranted.***

## Intervention Background & Overview

***Please provide relevant background information about the study agent(s) or intervention(s) that you are planning to use in the study. Include the following for each intervention:***

* ***FDA approval status (if applicable).***
* ***A summary of findings from non-clinical in vitro/in vivo studies that have potential clinical significance including information on mechanism of action, pharmacokinetics and safety. NOTE: This is particularly important for investigational agents, and may not be necessary for commercially available drugs, and/or drugs with sufficient clinical data.***
* ***A summary from relevant clinical studies (or current clinical use), with focus on those that provide background for your study.***
* ***Important safety information, such as known toxicities and current or approved doses and regimens.***
* ***If available (especially for early-phase or first-in-human trials): information on clinical pharmacokinetics, major route(s) of elimination, metabolism of the agent(s) in humans, and any potential for drug interactions.***

## Rationale for the Current Study

***Discuss the reasoning for conducting the study in light of the background information already presented. Specifically, provide rationale for each of the following:***

* ***The study design being used, including the primary endpoints.***
* ***The population being studied (particularly if focusing on a subset within the disease population, such as relapsed disease or elderly patients).***
* ***The treatment plan (particularly if doses and/or regimens are not established or will not follow approved versions).***

## Exploratory Studies

***If applicable, please provide background information to support any exploratory endpoints such as correlative studies; include the biological rationale and hypothesis (if applicable).***

# OBJECTIVES

***Please list all Primary, Secondary, and Exploratory objectives of the study (see below for definitions). Number objectives separately. In addition, it is strongly recommended that you have only one primary objective. An overall summary of the goal of the study is fine to include (e.g. “Establish the safety and efficacy of the combination of X and Y in the treatment of Z”), however specific objectives with measurable outcomes should be given to support this broad goal. These objectives and their corresponding results will be required to be entered into CT.gov.***

***This section should list the objective(s) only.*** [*Section 7*](#_Endpoint_assessment) ***will elaborate on the measurable outcomes and how evaluable patients will be defined.***

***An example of a clearly written objective is the following:***

The primary objective will be to assess the efficacy of drug ABC on reducing symptoms of depression in patients undergoing chemotherapy.

***Consider whether or not certain objectives are truly exploratory in nature (such as pharmacokinetics studies, tissue correlatives, etc.). It is strongly encouraged to label objectives that are not associated with health outcomes as exploratory.***

## Primary Objective

## Secondary Objectives

## Exploratory Objectives

*Delete if not applicable.*

Please see [Section 7](#_Endpoint_assessment) for endpoint assessment details, including relevant definitions and methods.

# PATIENT ELIGIBILITY

The target population for this study is patients with [insert description]. This will be a [multicenter or single-center] trial conducted at [insert name of site or clinic] of Northwestern University. *Remove or revise the following as appropriate:* Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include [list additional sites].

Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, or to the local PI at each participating site.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Patients must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Any questions or concerns regarding eligibility should be directed to the lead PI and assigned QAM. Study treatment may not begin until a patient is registered. Please refer to [Section 11](#_Registration_Procedures) for complete instructions regarding registration procedures.

*Highlighted sections below are CTEP recommendations on eligibility, based on the* [*broadened inclusion/exclusion criteria document released 9/26/2018*](https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm#policiesAndGuidelines)*. Please reference the linked document for guidance on how these criterion should be used.*

## Inclusion Criteria

*Each criterion should include its own number, e.g., 3.1.1, 3.1.2, etc. Inclusion criteria should not contain phrases that are actually meant to exclude patients (e.g. “patients must not have had prior radiation therapy”). This is actually an exclusion criteria and should be listed in* [*Section 3.2*](#_Exclusion_Criteria) *accordingly.*

### Patients must have a 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 [study disease]. *Specify eligible disease(s)/stage(s).*

*If study has an integral biomarker to determine eligibility to study or specific treatment arm(s), then the relevant eligibility criteria must be stated (e.g. Presence of [specific gene mutations and variants]).*

### Patients must have [measurable or evaluable] disease. See [Section 7](#_Endpoint_assessment) for the evaluation of measurable disease.

### Please state allowable type and amount of prior therapy. Define as appropriate any limitations on prior therapy and the time from last prior regimen (e.g., no more than 6 cycles of an alkylating agent; no more than 450 mg/m2 doxorubicin for agents with expected cumulative cardiotoxicity). Include separate definitions for duration as needed (e.g., at least 4 weeks since prior chemotherapy or radiation therapy, 6 weeks if the last regimen included BCNU or mitomycin C). Include site/total dose for prior radiation exposure as needed (e.g., no more than 3000 cGy to fields including substantial marrow).

### Patients must be age ≥ 18 years. Please modify for pediatric or other trials, as applicable.

### Patients must exhibit a/an [ECOG, Karnofsky, or other] performance status of [insert values].

### Patients must have adequate organ and bone marrow function as defined below: These are guidelines that may or should be modified based on protocol-specific or drug development-specific needs.

|  |  |
| --- | --- |
| Leukocytes (WBC) | ≥ 3,000/mcL |
| Absolute neutrophil count (ANC) | ≥ 1,500/mcL |
| Hemoglobin (Hgb) | ≥ 9 g/dL *(specify if transfusions allowed with timeframe)* |
| Platelets (PLT) | ≥ 100,000/mcL *(specify if transfusions allowed with timeframe)* |
| Total bilirubin | ≤ Institutional upper limit of normal (ULN) |
| AST (SGOT)/ALT (SGPT) | ≤ 3 x institutional ULN *(specify modifications for liver mets, as applicable)* |
| Creatinine, OR | ≤ Institutional ULN |
| Glomerular filtration rate (GFR)  eGFR is estimated GFR calculated by the abbreviated MDRD equation : 186 x (Creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if black) | ≥ 60 mL/min/1.73 m2 *unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73 m2* |

*NOTE: Include any exceptions to the above (such as Gilbert’s Syndrome) and note whether nor not levels may be achieved with transfusion and/or growth factor support.*

### For patients with a known history of Human immunodeficiency virus (HIV), infected patients on effective anti-retroviral therapy must have a viral load undetectable for 6 months prior to registration.

### For patients with a known history of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

### Patients with a known history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

### Patients with treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression. *(Note: In specific trials, it may be necessary to add a time factor regarding the follow-up brain imaging, but this should be as lenient as medically indicated. If CNS trial, this should be adjusted accordingly.) This criteria is not meant for trials designed for primary brain tumors or for brain metastases.*

### Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

### Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

### Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

### The effects of [Agent] on the developing human fetus are unknown. For this reason and because [Agent Class] agents as well as other therapeutic agents used in this trial are known to be teratogenic, females of child-bearing potential (FOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from time of informed consent, for the duration of study participation, and for # days following completion of therapy. Should a female patient become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception from time of informed consent, for the duration of study participation, and 4 months after completion of administration.

NOTE: A FOCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

* *Has not* undergone a hysterectomy or bilateral oophorectomy
* *Has had* menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)

### FOCBP must have a negative pregnancy test prior to registration on study.

### Other study-specific inclusion criteria or baseline parameters that are required for eligibility purposes (such as LVEF, QTc interval, disease-specific criteria, etc.).

### Patients must have the ability to understand and the willingness to sign a written informed consent document.

## Exclusion Criteria

### Patients who have had chemotherapy or radiotherapy ≤ 28 days (6 weeks for nitrosureas or mitomycin C) prior to planned treatment start date.

### Patients who have not recovered from adverse events due to prior anti-cancer therapy (i.e., have residual toxicities > Grade 1) with the exception of alopecia.

### Patients who are receiving any other investigational agents.

### The investigator(s) must state a medical or scientific reason if patients who have brain metastases will be excluded from the study.

### Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to [study agent(s)].

### Please state appropriate exclusion criteria and relevant windows relating to concomitant medications or substances that have the potential to affect the activity or pharmacokinetics of the study agent(s). Examples of such agents or substances include those that interact through the CYP450 isoenzyme system or other sources of drug interactions (e.g., P-glycoprotein). Specifically excluded substances may be listed below, stated in [*Section 9*](#_DRUG_INFORMATION) (Drug Information), and presented as an appendix. If appropriate, the following text concerning CYP450 interactions may be used or modified. Be careful if patients with metastases are allowed on trial and their use of steroids. Please clarify steroid use allowed on trial.

Patients receiving any medications or substances that are inhibitors or inducers of [specify CYP450 enzyme(s)] are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

### Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible: *(edit/remove/add to list as needed)*

* **Hypertension that is not controlled on medication**
* **Ongoing or active infection requiring systemic treatment**
* **Symptomatic congestive heart failure**
* **Unstable angina pectoris**
* **Cardiac arrhythmia**
* **Psychiatric illness/social situations that would limit compliance with study requirements**
* Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient’s safety or study endpoints

### Patients with psychiatric illness/social situations that would limit compliance with study requirements.

### Female patients who are pregnant or nursing. The investigator(s) must state a medical or scientific reason if pregnant or nursing patients will be excluded from the study. The full text of the Policies, Guidelines, and Procedures pertinent to this requirement is available on the CTEP website ([*http://ctep.cancer.gov/protocolDevelopment/policies\_pregnant.htm*](http://ctep.cancer.gov/protocolDevelopment/policies_pregnant.htm)). Suggested text is provided below:

Pregnant women are excluded from this study because [Agent] is [Agent Class] agent with 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 [Agent]*,* breastfeeding should be discontinued if the mother is treated with[Agent].

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

### Other study specific or disease criteria for exclusion (e.g. certain disease sub-types that are not eligible, patients who are unable to swallow oral medication if the study involves oral agents, etc.).

# TREATMENT PLAN

***As with all sections of this template, please delete sub-sections that do not apply and/or re-name to fit the specifics of your study.***

## Overview

***Give a brief (1-2 paragraphs at most) summary of the treatment plan, including intervention(s), doses/regimens, duration of treatment, and key study time-points (response assessment, futility assessment, transition from phase I to II if a combination study, etc.).* For any assessments completed prior to treatment start, that are also part of the eligibility criteria, patients must continue to meet full eligibility before initiating treatment on Cycle 1 Day 1.**

***If applicable, consider an appropriate timeframe in which patients should start treatment after registration/randomization. Be mindful of rapidly progressing disease and baseline imaging.***

## Treatment Administration

***It may be useful to include a table that summarizes the various interventions prior to giving details:***

***Consider pre-medication and supportive therapy specifics in cases of multi-institutional trials. How may these differ across sites and would it be appropriate for sites to differ slightly on such items? Consider standard of care administration across multi-institutional trials. Consider adding language “*per institutional practice*”, as applicable. Clarify if any items are required versus recommended. If using multiple agents, specify if one should occur before the other and/or if there is any lag time between those agents.***

***This section should comply with the permitted/prohibited*** [*Concomitant Medication Section*](#_Concomitant_Medications/Treatments)***.***

***Table 1: Treatment Administration Summary***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Treatment Administration Summary** | | | | | | |
| **Agent** | **Premedications** | **Dose\*** | **Route** | **Schedule** | **Cycle Length** | **Supportive Therapies** |
| Drug A | Acetaminophen 650 to 1000 mg every 4 to 6 hours for 3 days prior to Drug A | 300 mg/m2 | IV over 2 hours **before** Drug B (day 1 only) | Days 1, 8, and 15 of each cycle | 4 weeks (28 days) | Omeprazole or similar as needed |
| Drug B | N/A | 150 mg/m2 | IV 30 min after completion of Drug A (day 1 only) | Day 1 of each cycle | N/A |
| Drug C | N/A | 50 mg tablet | PO in the a.m. at least 1 hour before eating | Daily x 3 weeks followed by 1 week break per cycle | Switch to taking 1 hour after eating if vomiting occurs |

**\* Starting Dose**

### Intervention/Agent A

***Describe the intervention in detail, including the following:***

* ***Dose/route/schedule (if using cycles, define “cycle” for your trial)***
* ***Instructions for patients (if self-administered) or clinical staff (e.g. how to monitor)***
* ***Any required or recommended supportive care medications (include dose(s), instructions for how/when to administer, criteria for administration, etc.)***
* ***Methods for tracking compliance (e.g. pill diary-if using a pill diary, this must be created and IRB approved)***
* ***Instructions regarding skipped or missed doses***
* ***Infusion lengths including windows***
* ***Any required parameters for receiving treatment (i.e. on day 1 of each cycle)***
* ***Any required parameters for resuming treatment***

### Intervention/Agent B

### Intervention/Agent C

## Phase I Dose Escalation Scheme

***Remove this section & re-number others if this does not apply to your trial.***

***Studies with a Phase I portion may incorporate one of several statistical designs for dose escalation. Please consult with the assigned statistician on your study to determine what design is appropriate, and see separate attachment for example language.***

***Key items to include in this section:***

* ***State the starting dose(s) of the agent(s)/drug(s).***
* ***Explain escalation/de-escalation rules for each agent/drug (or indicate if certain agents/drugs are kept constant). Please note that escalation of only one drug at each dose level is recommended.***
* ***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.***
* ***Use tables to illustrate dose levels/cohorts. Use exact doses rather than percentages.***
* ***Consult with your biostatistician when designing your dose escalation scheme and rules!***

All study teams are expected to notify the Principal Investigator and assigned QAM when a DLT has occurred.

### Definitions

*Tips to consider:*

* ***Define the period during which patients will be evaluating for dose-limiting toxicities (DLT period).***
* ***Describe how DLTs will be evaluated (e.g. per CTCAE v 5.0 criteria or other).***
* ***Indicate whether or not toxicities must be related to study therapy to be labeled DLT (generally DLTs are defined as toxicities attributed to study therapy, but in some cases there may be exceptions to this).***
* ***Provide an explicit definition of what constitutes a DLT:***
  + ***Types or categories of toxicities (e.g. hematologic vs. non-hematologic)***
  + ***Grades (e.g. “any ≥ Grade 4”)***
  + ***Duration of events (e.g. “persisting for ≥ 1 week”)***
  + ***Clearly list any exceptions to the DLT definition (e.g. “any ≥ Grade 3 non-hematologic toxicity except for alopecia any grade”).***
* ***Clearly state the definition of MTD and (if appropriate) how this pertains to phase II (e.g. MTD will be the recommended phase II dose or RP2D).***

## Toxicity Management & Dose Delays/Modifications

*This section should be included in all protocols, including phase I (note that for phase I trials, this usually pertains to management of toxicities that do not meet the criteria of DLT).*

*Things to consider for this section:*

* *If more than one drug/agent is administered, provide a detailed description of toxicity grades and course of action for each agent separately. Also explain how to apply dose adjustments in the event that more than one study drug/agent could be responsible for a given toxicity, (e.g. “For non-hematologic toxicities, adjust Drug B before Drug A”).*
  + *With this in mind, indicate if certain drug doses should be skipped or delayed and how the remaining agents/interventions should continue*
* *Indicate if and/or when treatment modifications are appropriate (if not permitted, please state when that is the case and reference the appropriate section for how to manage the patient once they are off study therapy)*
* *If dose modifications are anticipated/allowed, provide a dose de-escalation scheme (table) for intra-patient dose adjustments. Please also address whether and when re-escalation is permitted, and in what fashion.*
  + *What happens to patients after the lowest dose is administered?*
* *For guidance, refer to the appropriate sections in the protocol that contain more detailed information on the known or potential toxicities associated with each drug/agent.*
* *Use tables rather than lengthy blocks of text!*
* *Dose adjustments should be expressed using* ***exact doses rather than percentages****.*
* *If dose delays or omissions are allowed:*
  + *Specify if/when study treatment may resume and at what dose (e.g. “Hold until resolved to ≤ Grade 1 or baseline and then resume at same dose level”).*
  + *Indicate how many days or doses/cycles of treatment may be missed before patient must be removed from the study.*
* *For ease of reading, dose modifications may be divided into hematological versus non-hematological criteria. For hematological toxicity, please address guidance on use of growth factor support.*
  + *Be mindful of the eligibility lab criteria used to get patients on trial. Consider looking at the change in baseline in determining the dose modifications.*
* *If applicable, include supportive care actions to be taken aside from holding therapy or adjusting doses (e.g. “administer Agent B as needed and refer to cardiologist for evaluation”).*

*The following tables are provided as examples and should be modified as appropriate:*

*Table 2: Dose Modifications*

| **Toxicity** | **Grade/Description** | **Drug A** | **Drug B** |
| --- | --- | --- | --- |
| **Hematologic Toxicities** | | | |
| Thrombocytopenia | Grade 1 or 2 | Maintain dose level. | Maintain dose level. |
| Grade 3 or 4 | 1st occurrence: Hold dose & follow CBC weekly. Once ≤ Grade 1 (platelets ≥ 75,000/mm3), resume at same dose.  2nd occurrence: Hold dose & follow CBC weekly. Once ≤ Grade 1 (platelets ≥ 75,000/mm3), resume at 1 dose level lower. | Hold Drug B if Drug A is held; resume Drug B at same dose once Drug A resumes (regardless of whether or not Drug A dose is changed). |
| Neutropenia | Grade 1 or 2 | Maintain dose level. | Maintain dose level. |
| Grade 3 w/ fever or Grade 4 | 1st occurrence: Hold dose & follow CBC weekly. Once resolved to > 1.0 x 109/L (if neutropenia was the only toxicity noted), resume at same dose. If other toxicity was noted, resume at 1 dose level lower.  2nd occurrence: Permanently discontinue Drug A. | Maintain dose level. If Drug A is permanently discontinued but patient is receiving benefit, may consider continuing on single-agent Drug B, per treating investigator’s discretion. |
| **Non-hematologic Toxicities** | | | |
| Allergic reaction or hypersensitivity | ≤ Grade 3 | Hold dose until resolved to ≤ Grade 1 & then resume at same dose level. | Hold dose until resolved to ≤ Grade 1 & then resume at same dose level. |
| Grade 4 | Permanently discontinue Drug A. | Permanently discontinue Drug B. |
| Infection | ≥ Grade 3 | Hold dose until systemic treatment for infection is complete. If no neutropenia, resume at same dose level. If neutropenic, follow instructions above (hematologic section).  If no resolution after > 3 weeks: permanently discontinue Drug A. | Hold dose until systemic treatment for infection is complete. If no neutropenia, resume at same dose level. If neutropenic, follow instructions above (hematologic section).  If no resolution after > 3 weeks: permanently discontinue Drug A. |
| Herpes zoster or simplex | Any grade | Maintain dose level. | Hold dose until lesions are dry & then resume at same dose level. |
| Neuropathy | Grade 2 w/ pain or Grade 3 | Initially, maintain dose level. If neuropathy persists for > 2 weeks, hold dose until resolved to ≤ Grade 2 or baseline then resume at 1 dose level lower. | May continue on single-agent Drug B (per treating investigator’s discretion) if Drug A is held. Maintain dose level. |
| Grade 4 | Permanently discontinue Drug A. | If patient is receiving benefit, may continue on single-agent Drug B (per treating investigator’s discretion) if Drug A is discontinued. Maintain dose level. |
| Renal dysfunction | CrCl ≤ 15 mL/min | Hold dose until CrCl > 15 mL/min & then resume at 1 dose level lower. | Hold dose until CrCl > 15 mL/min & then resume at 1 dose level lower. |
| Other | Grade 1 or 2 | Maintain dose level. | Maintain dose level. |
| Grade ≥ 3 | Hold dose until resolved to ≤ Grade 1 or baseline. Once resolved, resume at same dose level.  Unresolved (persisting > 2 weeks) or recurrent event: permanently discontinue Drug A. | Hold dose until resolved to ≤ Grade 1 or baseline. Once resolved, resume at same dose level.  Unresolved (persistent > 2 weeks) or recurrent event: permanently discontinue Drug B. |

## Concomitant Medications/Treatments

*Please list all relevant concomitant drugs and/or treatments that are required, allowed, or prohibited (sub-sections should be used), and any resulting study drug modifications. Consider herbal supplement restrictions. Consider any rare cases of minor or elective surgeries or palliative radiation and if these are allowed and/or what to do in these situations (i.e. consult with lead PI or DSMC; hold drug for how long).* If trial eligibility requires measurable disease at baseline, then any surgeries and/or palliative radiation should not be used to treat target lesions. If additional surgery, radiation, and/or systemic therapy is required for patient safety, then the patient should be taken off treatment. *The timeframe for collecting concomitant medications should be included here (consistent with* [*Section 5.0*](#_STUDY_PROCEDURES)*). This section should be consistent with restrictions and windows in the inclusion/exclusion criteria, as well as any pre-medications that are required or recommended. If any medications may be used, but only with caution, please clearly address that in this section. Be mindful of steroid use especially for immunotherapy trials.*

## Other Modalities or Procedures

*If applicable, please provide a description of any other modalities (e.g., surgery, radiotherapy) or procedures (e.g., hematopoietic stem cell transplantation) used in the protocol treatment. Please distinguish between those modalities that comprise standard of care, and those under investigation within your protocol (if standard of care, the description does not have to be lengthy but should include information relevant to the study, such as timing or other requirements).*

## Duration of Therapy

*This section should clearly define the “end of protocol therapy.” This may be a clearly defined number of cycles or doses, or it may be open-ended with specific criteria to determine when treatment will conclude. Refer to removal criteria in* [*Section 4.9*](#_Removal_of_Patients) *when appropriate.*

*The following language is recommended for immunotherapy trials that use RECIST 1.1 that wish to treat beyond initial progression:*

At the time of official determination, in the event of an initial assessment of PD (based on RECIST Version 1.1), a patient may continue to receive the assigned study treatment as long as none of the criteria listed below are met.

1. Confirmed PD: An initial assessment of PD by RECIST 1.1 or Lugano criteria will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later (see [Section 7](#_Endpoint_assessment)). If any subsequent tumor assessment shows progression per RECIST v1.1 or Lugano criteria in the overall tumor burden (the sum of diameters of target lesions and new lesions), when compared to the initial PD assessment (the sum of diameters of target lesions and new lesions), then PD is confirmed.
2. Meets any of the other investigational product discontinuation criteria ([Section 4.7](#_Duration_of_Therapy))
3. Clinical symptoms or signs indicating significant PD, for example the benefit-risk ratio of continuing therapy is no longer justified.
4. Decline in *ECOG* performance status.
5. Threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention, and continuation of study therapy would prevent institution of such intervention.

## Duration of Follow Up

*This section should clearly define the protocol-specific follow-up period and nature.*

*Things to consider:*

* *All studies should have an end of treatment visit (which may or may not also be end of study) approximately 30 days after the last dose of study drug for the purposes of adverse event assessment.*
* *Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.*
* *Follow-up behind the 30-day post-last-dose visit will depend on study endpoints and individual sponsor requirements; patients may need to be followed to document disease progression or start of next therapy or survival.*
* *If there are no long-term endpoints, it is not necessary to state when and how patients will be followed clinically for disease management behind the end of study visit. This section pertains only to the period during which data is still to be collected for patients on this study for study purposes.*
* *Please think this through carefully as following patients until death may require considerable resources, and may not be necessary (although if this will definitely be the case, please clearly state such).*
* *Include the nature (i.e. survival tracking only) and frequency of follow-up (e.g., visits every 3 months, by phone call every 6 months, etc.).*

## Removal of Patients from Study Treatment and/or Study as a Whole

*The language below is somewhat standard and should be modified as appropriate for the study under development:*

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

**Criteria for Removal from Study Treatment**:

* Patient meets any of the stopping points per [Section 4.7](#_Duration_of_Therapy) (*delete bullets already listed in* [*Section 4.7*](#_Duration_of_Therapy))
* Patient voluntarily withdraws from treatment (follow-up permitted)
* Patient withdraws consent (no follow-up permitted)
* Patient is unable to comply with protocol requirements
* Patient demonstrates confirmed disease progression
  + If appropriate, include a definition of disease progression (i.e. clinical vs. radiological progression as defined by RECIST v 1.0).
* Patient demonstrates clinical progression
* Intercurrent illness that prevents further administration of treatment
* General or specific changes in the patient’s condition that renders the patient unacceptable for further treatment in the judgment of the investigator
* Patient develops a second malignant neoplasm
* Patient experiences unacceptable toxicity
* Patient’s study therapy is delayed beyond the allowed period [## days]
* Treating physician determines that continuation on the study would not be in the patient’s best interest
* Patient becomes pregnant
* Patient develops a second malignancy that requires treatment which would interfere with this study
* Patient becomes lost to follow-up (LTF) per institutional standard
* Termination of the study by Sponsor
* The drug manufacturer can no longer provide the study agent

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

**Off Study Criteria:**

* Death
* Lost to follow-up
* Patient enrolls on another therapeutic clinical trial
* Withdrawal of consent for any further data submissions
* Follow-up period is met as outlined in the protocol

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in NOTIS and NOTIS eCRFs.

# STUDY PROCEDURES

*In calculating days of tests, the day a test is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. If a Day falls on a weekend or holiday, the limit may be extended to the next working day. The table below is provided as an example only and should be modified as appropriate to fit the study under development. Column headings can be changed, added, removed, or combined. Procedures and activities should be listed in the far left column. Use of footnotes to provide clarity and detail is strongly encouraged.*

* *Include windows (ideally at column headings), specifying treatment vs. assessment window differences if applicable*
* *For laboratory procedures, please indicate the assessment based on lab order*
  + *If thyroid tests included, specify TSH only vs. w/ reflex testing*
  + *If hepatitis testing is required, consider what specific tests are needed. For example: “Hepatitis testing at screening will include HBcAb, HBsAg, HBsAb, and Hepatitis C antibody – patients who are positive for HBcAb, HBsAg, or Hepatitis C must have a negative PCR prior to enrollment”*
* *For laboratory procedures, please consider how long these tests take to result and if they are needed prior to each dose*
* *Please consider imaging restrictions (i.e. contrast allergies) when describing imaging*

*\*\*\*Formatting tip for the study procedures table to fit on one page (landscape): Place the curser at the beginning of Section 5. Go to Page Layout, Breaks, under Section Breaks select Next Page. Then place the curser at the end of Section 5. Go to Page Layout, Breaks, under Section Breaks select Next Page. This allows Microsoft Word to understand that Section 5 will have its own formatting. Lastly, place the curser anywhere within Section 5. Go to Page Layout, Orientation, and select Landscape. This should make only section 5 landscape, while the remainder of the protocol remains as portrait.\*\*\**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Screening1 | | | On Treatment10, 11 | | Off Treatment | |
| Time Period | **Baseline** | **Cycle 1**  **(± # days)** | **Cycle 2+**  **(± # days)** | | **Every 3 cycles**  **(± # days)** | **End of Treatment12**  **(± # days)** | **Follow-up13** |
| Assessment or Activity |  | | | | | | |
| Informed Consent | X |  |  | |  |  |  |
| Medical history | X |  |  | |  | X |  |
| Physical exam | X | X | X | |  | X |  |
| Vital signs2 |  |  |  | |  |  |  |
| ECOG status | X | X | X | |  | X |  |
| Con Meds | X | X | X | | X | X |  |
| Toxicity assessment |  | X | X | | X | X |  |
| Tumor Measurements3 | X |  |  | | X | X |  |
| CBC with diff4 | X | X | X | |  | X |  |
| Chemistry panel5 | X | X | X | |  | X |  |
| Pregnancy test6 | X |  |  | |  |  |  |
| Correlatives7 |  |  |  | |  |  |  |
| Drug A administration8 |  | X | X | |  |  |  |
| Drug B administration9 |  | X | | | |  | |
| Survival status |  |  |  | |  |  | X |

1 *Include general timing for the screening period. Any exceptions to this timeframe should be denoted with a separate footnote (for example, in a 28-day screening period, there may be longer allowances for informed consent and scans, or shorter requirements for labs).*

2 Includes vital signs *(include any specific requirements such as pulse, blood pressure)* and height (baseline only) and weight.

3 *Specify modality for imaging as well as specific timeframes and imaging sites (if applicable).* The same modality used at baseline should be used throughout.

4 CBC w/ differential *(include any specific requirements, such as ANC, WBC, platelets, hemoglobin)*

5 Chemistry panel *(spell out chemistry panel tests; if any special tests are needed that are not included in the chemistry, consider adding a separate row, for example PT/INR, TSH, LDH, Magnesium, Phosphorus, Uric Acid).*

6 Serum or urine test for females of child-bearing potential. *Check with sponsor for pregnancy requirements and language. At a minimum, pregnancy should be checked at baseline / prior to treatment.*

7 *Please include timing of correlative sample collections, separated by type of samples (e.g. blood, tissue).* Refer to [correlative section](#_CORRELATIVES/SPECIAL_STUDIES) / lab manual for further details.

8 *Please include general details on dosing for each drug, including route, timing, and assigned dose.*

9 *For oral drugs, include general dosing instructions, including drug accountability and diary review.*

10 Treatment should start ≤14 days after patient registration.

11 A cycle is defined as 21 days (+/- 2 days).

12 *Please include timing of End of Treatment visit. This is often dictated by a required safety reporting period provided by the funding source. Without any guidance, a period of 30 days (±7 days) is recommended.*

13 *Please specify frequency and length of follow-up once patients have completed treatment. The timeframe and procedures should be determined by study endpoints. For example:* Patients will be followed (either by routine clinic visit or by phone call) every 3 months for 2 years and then every 6 months up to 5 years total from start of study treatment to document survival and disease progression.

# CORRELATIVES/SPECIAL STUDIES

*Summarize the goal/rationale of the planned laboratory correlative studies.*

*In addition, please list each correlative study in the table below with the required information. The Protocol Development Coordinator will format the information as needed in the subsequent sections of the protocol as well as a separate lab manual. If there are no correlative/special studies, remove this section entirely and re-number remaining sections.*

*A more detailed table will need to be filled out prior to the SIM. Prior to SRC the table will then be condensed, ensuring analysis to be performed and the approximate volume of blood is left in the protocol. Please refer to Correlative Job aid for tips on how to complete this section.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Correlative Samples - Details for Lab Manual**  *Please add additional rows as needed or mark “N/A” where information does not apply* | | | |
| **Correlative study (sample type)**  ***e.g. Pharmacokinetics (blood)*** |  |  |  |
| **Mandatory or Optional** |  |  |  |
| **Timing (+/- windows)** |  |  |  |
| **Volume Needed (blood only)** |  |  |  |
| **Tube type needed (blood only)** |  |  |  |
| **Tissue thickness and/or # slides (tissue only)** |  |  |  |
| **Processing center (e.g. PCF-CTU)** |  |  |  |
| **Sample handling/processing instructions** |  |  |  |
| **Shipping/delivery info** |  |  |  |
| **Storage needs** |  |  |  |
| **Analysis center** |  |  |  |
| **Assay methodology** |  |  |  |

## Sample Collection Guidelines

## Sample Processing, Storage, and Shipment

## Assay Methodology

## Specimen Banking

# Endpoint assessment

***For each objective listed in*** [*Section 2.0*](#_OBJECTIVES)***, please describe the corresponding endpoint, which is related to the outcome that is being measured. This includes what will be measured, how, and when. In addition, there are generally 4 levels of specificity that should be included:***

* **Level 1 – Domain or the type of health outcome measure.**
* **Level 2 – Specific tool to measure the domain.**
* **Level 3 – Specific metric to be measured.**
* **Level 4 – Method of aggregation (continuous vs. categorical).**

***An example of a clearly written endpoint is the following:***

EXAMPLE 1: To determine the overall response rate (ORR) by RECIST v 1.1 criteria for the combination of [Agent].

To address the primary objective, 2 or more responses (CR or PR) out of 11 are needed in

Stage 1 to continue the trial to the full 30 patients. If the trial continues to the full 30 patients, then ORR will be estimated using a two stage method.

Evaluable patient: A patient needs to have taken one dose of either study drug, and completed the first scan to be evaluable for this primary endpoint.

EXAMPLE 2: To determine progression free survival by RECIST v1.1 criteria, as well as 1-year, 2-year, and median overall survival with [Agents].

Evaluable patient: Any patient who has taken one dose of either study drug will be evaluable for this endpoint.

EXAMPLE 3: To determine safety and tolerability of [Agents] as determined by NCI CTCAE v 4.03.

Evaluable patient: Any patient who has taken one dose of either study drug will be evaluable for this toxicity endpoint.

***Other examples of common endpoints and things to consider:***

* ***Response – often a primary endpoint for phase II trials***
  + ***Specify which criteria will be used (e.g. RECIST, Cheson, iwCLL2008, etc.)***
  + ***Specify how it will be reported:***
    - ***By response category (e.g. CR/PR/SD/PD or some combination of these)***
    - ***In terms of time or “duration of response”***
* ***Survival – often used in phase II or III trials***
  + ***Specify the type (e.g. progression-free or overall survival) and at what time point (e.g. indefinitely vs. at 2 years from start of treatment)***
* ***Safety/toxicity – often used in phase I or II trials***
  + ***Specify what criteria will be used (e.g. NCI CTCAE v 5.0) or if the focus will be on a specific list of adverse events of interest***
* ***Quality of life – may be a secondary or even exploratory endpoint in any trial***
  + ***Specify the subjective measure that will be used (if it is a tool or survey, briefly describe in background and indicate if it has been validated)***

*Clearly state which patients will be considered evaluable for each endpoint!*

*If appropriate, include guidelines describing when and how enrolled patients will be considered evaluable in the study, and the actions to be taken when not (full patient replacement or addition of another patient).*

*For example in a safety/toxicity endpoint:*

“If a patient is enrolled but comes off study before Cycle 1 Day 1 of treatment, the patient may be replaced.”

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

## Primary Endpoint

*Describe the primary endpoint, including how (what methods) and when (specifically) it will be assessed. For example, if response rate is an endpoint, note at what time point(s) this is assessed for all patients (i.e. after every 2 cycles or at 6 months post-end of therapy).*

*If there is published criteria to be utilized (iwCLL, RANO, RECIST, others) describe the criteria and include descriptions or refer to table representations in the appendices.*

*Clearly state which patients will be considered evaluable for each endpoint!*

## Secondary Endpoints

*Same as with primary endpoints:*

* *Define*
* *Explain how and when each will be assessed*
* *Note the relevant criteria (or tools, such as FACT-Fatigue questionnaire)*
* *Clearly state who will be evaluable for each endpoint*

## Exploratory Endpoints

*Same as with primary endpoints:*

* *Define*
* *Explain how and when each will be assessed*
* *Note the relevant criteria (or tools, such as FACT-Fatigue questionnaire)*
* *Clearly state who will be evaluable for each endpoint*

## Definitions

*Define/describe any terminology that is used in study endpoints or to address the objectives of the study (i.e. MTD, response categories, PFS/OS, etc.). Include definitions (if applicable) of measurable vs. evaluable disease using sub-sections for each endpoint as needed.*

# STATISTICAL CONSIDERATIONS

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

## Study Design/Study Endpoints

*Please specify the study design. Clearly state design aspects (i.e. retrospective or prospective, blinded, randomized, single or multi-centered). Define all study endpoints.*

*If there are stopping rules for either safety or efficacy, describe the reasoning behind them, and how they might cause a suspension of study enrollment until a safety review has been convened.*

## Sample Size and Power Analysis

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

## Accrual and Feasibility

*Include a monthly accrual rate along with number of sites and potential screening rate to justify feasibility.*

## Data Analyses Plans

*Please describe in detail how each objective will be addressed by a particular data analysis plan. This is where the details of each data analysis plan (for each objective) are given – stating what statistical methods will be used, and under which assumptions. Every objective/study endpoint should have a plan associated with it.*

# DRUG INFORMATION

***The details in this section should be repeated for each agent administered (including standard of care therapies).***

## Agent [Here]

### Other names

### Classification - type of agent

### Mode of action

### Storage and stability

### Protocol dose specifics

*If a drug is given at different doses at different points in the treatment cycle, all doses should be indicated. If standard/approved dosing is used, please refer to package insert.*

*For oral drug, please include whether drug needs to be dispensed in the original container or if we need to count exact number of tablets and put them in an empty vial for dispensing. We usually dispense full bottles when we can.*

### Preparation

*If investigational, include preparation instructions. If standard/approved dosing is used, please refer to package insert. If oral, it is acceptable to state that no preparation is required.*

*Include whether any specific type of IV bag needs to be used (PVC vs non-PVC for example) and what solution is required (NS vs. D5W). Is there any special tubing that needs to be used? Important to specify whether overfill and amount of drug added need to be removed when preparing an IV dose. How should prepared dose be stored (refrigerator vs room temp) and what is the expiration? Does it need to be protected from light?*

### Route of administration for this study

### Incompatibilities

### Side Effects

*List adverse events by category (i.e. “Most Likely” vs. “Less Likely” vs. “Rare or Serious” or use percentage cut-offs). This must be done by the PI and he/she should verify that this reflects the IB or package insert for each drug. This will be the basis for the consent form risk section so it is essential that this be correct.*

Please refer to the current [Investigator’s Brochure (IB) or Package Insert] for a complete listing of all toxicities.

### Availability & Supply

*Specify if commercially available and not supplied by study or if provided by sponsor (if provided but will be commercial supply, state this as it affects the IND). Include contact information and instructions for ordering drug (may refer to stand-alone order form). For multi-center trials, specify if drug is shipped directly to each site or if all will come to NU and then be shipped out.*

### Return and Retention of Study Drug

*Information regarding retention of used vials should be stated here. Information regarding Funding Sponsor policy on expired drug, drug returns during the course of trial by patient, and drug returns at end of study should be stated here. Unless otherwise specified, the Standard Operating Procedures of the Investigational Pharmacy will be followed.*

### Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents provided by the Study. Store and maintain separate Drug Accountability Records (DARF) for each agent. *Specify if accountability logs will be provided by Funding Sponsor or if internal NMH logs can be used. Specify if there are kit numbers assigned or an electronic randomization system (e.g. IWRS) to be utilized for ordering and/or dispensing drug.*

# ADVERSE EVENTS

## Adverse Event Monitoring

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

## Definitions & Descriptions

### Adverse Event

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

All routine AEs, regardless of attribution or clinical significance, occurring from time of registration, through 30 days after the last administration of study drug, must be recorded. See [Section 10.3.1](#_Routine_Reporting) for instructions on recording routine AEs.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms, referencing CTCAE when applicable. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). *Please note that medical history and preexisting conditions will be recorded on the Adverse Event eCRF in order to establish if the event worsened while on study and thus qualifies as a reportable adverse event.* Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

#### Adverse Event Assessment

*Note, some hematology studies may choose to grade toxicity using alternatives to the CTCAE v5.0 (e.g., iwCLL criteria). When an alternative is used, please modify this section as needed. If using the CTCAE state:*

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly as an adverse event or expedited adverse event, as applicable.

1. Identify the type of adverse event using the NCI CTCAE v 5.0.
2. Grade the adverse event using the NCI CTCAE v 5.0.
3. Determine whether the adverse event is related to the protocol therapy.

* Attribution categories are as follows:
  + Definite: AE is *clearly related* to the study treatment.
  + Probable: AE is *likely related* to the study treatment.
  + Possible: AE *may be related* to the study treatment.
  + Unlikely: AE *not likely to be related* to the study treatment.
  + Unrelated: AE is *clearly NOT* *related* to the study treatment.

1. Determine the prior experience of the adverse event.

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

* the current protocol
* the drug package insert
* the current Investigator’s Brochure

#### Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at <https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>

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

* Mild (grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
* Moderate (grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL\*.
* \*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
* Severe (grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL\*\*.
  + \*\*Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
* Life-threatening (grade 4): Life-threatening consequences; urgent intervention indicated.
* Fatal (grade 5): Death related to AE.

### Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence. See [Section 10.3.2](#_Expedited_Reporting_of) for instructions on reporting SAE’s.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

* Results in *death*.
  + If death results from (progression of) the disease, should be reported as **Grade 5 “disease progression”** in the system class “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
* Is *life-threatening*.

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

* Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.
* Results in *persistent or significant disability or incapacity*.
* Is a *congenital anomaly/birth defect.*
* Any *important medical event* that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

### Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

* is *unexpected* (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied
* is *related or possibly related* to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
* suggests that the research places human subjects or others at *a greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has actually occurred.

## Adverse Event Reporting

### Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study’s phase and risk level, as outlined in the [DSMP](https://www.cancer.northwestern.edu/docs/research/data-safety-monitoring-plan.pdf).

### Expedited Reporting of SAEs/Other Events

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via expedited reporting via the NU CTO SAE Form. On the “Seriousness Criteria” drop down box of the SAE Form, select “Pregnancy.” Any pregnancy occurring in a patient or patient’s partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome.

#### Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CTO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

* Protocol description and number(s)
* The patient’s identification number
* A description of the event, severity, treatment, and outcome (if known)
* Supportive laboratory results and diagnostics
* The hospital discharge summary (if available/applicable)
* Country of incidence

All SAEs will be reported to, and reviewed by, the DSMC, per the [DSMP](http://cancer.northwestern.edu/docs/research/data-safety-monitoring-plan.pdf).

All expedited events require both expedited reporting and routine reporting.

#### Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University) and to participating sites whom have reporting responsibilities to Northwestern University. Participating sites should follow their local IRB guidelines for reporting to their local IRBs.

* Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
* Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to Northwestern University and to the NU IRB within 5 working days of notification.
* Information pertaining to an NU subject that fits into any of the categories listed on the Reportable New Information page will be reported to the NU IRB within 5 business days of knowledge or notification

#### Reporting to the FDA

*In the event that an IND is granted for this study, the following notifications will be handled by the NU QAM (if the protocol is determined to be IND exempt, this section will not apply):*

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but not fatal or life-threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

#### Reporting to [insert name of funding source(s)]

*Most drug companies and other funding sources have established procedures and policies for what events must be reported to them and when. It is NU Cancer Center Policy to utilize our CTO SAE Form for all reporting (companies may review and ask for additional items or forms if absolutely necessary). At a minimum, this section should state what events are to be reported, in what timeframe(s), and the contact person or method for reporting (i.e. phone, fax, e-mail). This section should state whether the Funding Sponsor wishes to receive a copy of ALL expedited events, or only those attributed to their study product.*

# STUDY MANAGEMENT

## Institutional Review Board (IRB) Approval and Consent

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

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

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

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

## Amendments

Amendments to the protocol will be initiated and maintained by the assigned Medical Writer. Requests for revisions may come from multiple sources, including but not limited to the Principal Investigator, study team, drug company, or FDA. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by [insert Funding Sponsor name if applicable]. Amendments will be distributed by the lead institution (Northwestern) to all participating sites upon approval by the Northwestern University IRB.

## Registration Procedures

*The following sub-sections should be kept for studies with both a Phase I and Phase II component. For all other studies, please keep only the applicable language and delete sub-headings. Consider an appropriate timeframe in which patients should start treatment after registration/randomization.*

### Registering a Patient – Phase I, select Pilot, Safety Run-In Trials

For potential patients for phase I, select pilot, or safety run-in studies, study teams are asked to inform the assigned QAM ([croqualityassurance@northwestern.edu](mailto:croqualityassurance@northwestern.edu)) of the date and time that the patient will need to be registered.

BEFORE a patient can be treated on study, the following items must be completed and submitted to confirm eligibility and receive an identification number:

* Patient’s signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
* Copy of the pathology report (upload to NOTIS)
* Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The assigned QAM will review all source documentation required to confirm eligibility that is readily available in the patient’s electronic medical record (EMR). Any information that is not available in the EMR must be de-identified and emailed to the QAM. Once the QAM confirms the patient is eligible, he or she will register the patient, assign a subject identification number, provide a cohort assignment (as applicable), and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

### Registering a Patient – Phase II, Phase III, select Pilot Trials

For potential patients for phase II/III and select pilot studies, study teams are asked to inform the assigned QAM ([croqualityassurance@northwestern.edu](mailto:croqualityassurance@northwestern.edu)) of the date and time that the patient will need to be registered.

BEFORE a patient can be treated on study, the following items must be completed and submitted to confirm eligibility and receive a subject identification number:

* Patient’s signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
* Copy of the pathology report (upload to NOTIS)
* Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The assigned QAM will review the registration documents. Once review is complete, he or she will register the patient, assign a subject identification number, provide a cohort assignment (as applicable) and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

## Data Submission

Data collection for this study will be done through [NOTIS](https://notis.fsm.northwestern.edu). Access to the trial in NOTIS is granted to appropriate roles identified at the time of participating site activation, or upon request. Site users will not be able to access the study in NOTIS until all required and study specific trainings are completed.

Once a patient is confirmed and registered to the study, eCRFs should be submitted according to the study procedures table. Generally, all data for phase I patients, or any safety run-ins during the time period patients are evaluated for Dose Limiting Toxicities (DLTs) must be submitted on a weekly basis. Generally, for all phase II/III patients, data are due with 10 days of a visit or end of cycle. A set amount of data may also be requested for any screen failures, as is defined by the study. In most instances, this will include collection of adverse events and baseline data from the time of registration to the date of screen failure.

## Instructions for Participating Sites

*Remove this language if no additional sites are planned.*

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office at Northwestern University (as applicable):

* Completed feasibility assessment(s) to verify site’s capacity to support a Northwestern sponsored trial
* Signed copy of Northwestern University’s Data Participating Site Acknowledgement which details data submission guidelines
* Draft consent form for review and approval prior to submission to the local IRB
* A copy of the official IRB approval letter for the protocol and informed consent
* A copy of the IRB approved informed consent
* Pertinent credentials (CVs, MLs, CITI & GCP Training and FDFs) for the local PI and any sub-investigators who will be involved in the study at the site
* Form FDA 1572 appropriately filled out and signed with appropriate supporting certifications

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training, and delegation of authority log). Full requirements will be outlined in the study start-up packet upon successful completion of a feasibility assessment.

## Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan ([DSMP](https://www.cancer.northwestern.edu/docs/research/data-safety-monitoring-plan.pdf)) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to the CTO website for additional information). The level of risk attributed to this study requires [insert monitoring level established during the Study Implementation Meeting (SIM), or as specified in SRC approval letter for LOI], as outlined in the [DSMP.](http://cancer.northwestern.edu/docs/research/data-safety-monitoring-plan.pdf) The assigned QAM, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

## Adherence to the Protocol

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

### Emergency Modifications

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

For any such emergency modification implemented, a modification must be submitted to the NU IRB within 5 business days of making the change, and the assigned QAM must be notified within 24 hours of such change. Such modifications also need to be reported to the FDA, as applicable, within the appropriate timelines.

### Other Protocol Deviations

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 Institutional Review Board (IRB). Protocol deviations must be reported according to the policies and procedures of the IRB of record.

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

* Has harmed or increased the risk of harm to one or more research participants
* Has compromised the rights and welfare of the research subject
* Has damaged the scientific integrity of the data collected for the study
* Results from willful or knowing misconduct on the part of the investigator(s)
* Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies

All protocol deviations will be documented by the study team on a paper or electronic deviation tracking log (see [NOTIS](https://notis.fsm.northwestern.edu/) for copy of log) as they occur. The deviation tracking log must be made available upon request for review by the assigned QAM. The deviation tracking log must be reviewed, signed, and dated by the investigator prior to each monitoring visit, or otherwise in a timely manner, whichever occurs first. The PI signed and dated deviation tracking log will be uploaded to eCRFs prior to each scheduled monitoring visit or upon request.

Deviations will be reviewed per the [DSMP](https://www.cancer.northwestern.edu/docs/research/data-safety-monitoring-plan.pdf).

## Investigator Obligations

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

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the [DSMP](https://www.cancer.northwestern.edu/docs/research/data-safety-monitoring-plan.pdf).

## Publication Policy

*This section should be removed if the trial is not rated as a high intensity trial.*

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study’s primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study’s biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

# REFERENCES

# APPENDICES