Clinical Trial Template Instructions:

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

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

The sections/language in **BLUE** are examples and/or instructions and should be modified. DELETE any sections that do not apply. When the document is complete all the sections in **BLUE** should either be omitted or modified to the specifications of your study.

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

**Principal Investigator:** Name

Institution

Address

(Phone)

(Fax)

Email

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

Name

Department/Division

For off-site sub-Is include:

Name

Institution

Address

(Phone)

(Fax)

Email

**Biostatistician:** Name

Institution

Address

(Phone)

(Fax)

Email

**Medical Monitor:** Name

Institution

Address

(Phone)

(Fax)

Email

**Study location(s):** list sites where study will be conducted

**Sponsor:** University of Arkansas for Medical Sciences(holder of the IND/IDE)

**Funding Source**: List support (funding or investigational agent from Pharmaceutical Company(ies) or other source (provide grant number, if applicable.)

**Version No.:** [version number]

**Version Date:** [date]

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# LIST OF ABBREVIATIONS

Examples Include:

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

# STUDY SCHEMA

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

Text Box: Total N:  Obtain informed consent. Screen subjects by criteria; obtain history, document. Flowchart: Extract: Randomize. Oval: N subjects Arm 1. Oval: N subjects Arm 2. Text Box: Perform pregnancy test; collect blood for assays;
Administer Study Product/Intervention. Text Box: Clinical and AE assessment. Text Box: Clinical and AE assessment. Flowchart: Decision: Assessment of Final Study Outcome Measures.

# STUDY SUMMARY

May be presented in narrative format (similar to a manuscript abstract) or as a summary table (see example below).

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

# BACKGROUND AND RATIONALE

## Disease Background

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

## Investigational Product Background

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

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

## Rationale

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

## Correlative Studies

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

# STUDY OBJECTIVES

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

Statement of purpose: e.g., to describe, to measure, to compare, to estimate

General purpose: e.g., efficacy, safety, immunogenicity, pharmacokinetics

Specific purpose: e.g., dose-response, superiority to placebo

## Primary Objectives

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

A typical primary objective for a phase I trial is:

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

Each objective (whether primary, secondary or exploratory) should receive a separate number and should have a corresponding endpoint described below in section 5.4.

## Secondary Objectives

Typical secondary objectives for a phase I trial include:

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

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

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

## Exploratory Objectives

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

## Endpoints

Specify which primary endpoint(s) will be used to answer your primary objective, and which secondary endpoints will be used to address your secondary objectives. Endpoints should also be described for exploratory objectives as well. A typical endpoint for the primary objective example in 5.1 would be “DLT will be defined based on the rate of drug-related grade 3-5 adverse events experienced within the first 8 weeks (2 cycles) of study treatment. These will be assessed via NCI’s CTCAE v4.0 toxicity criteria. The MTD will be defined, etc.”

# STUDY POPULATION

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

## Inclusion Criteria

Consider whether each criterion will be based on medical history, self-report, or whether screening tests will be required to evaluate eligibility.

For example:

* Diagnosis/disease status
* Allowable type and amount of prior therapy
* Age ≥ 18 years.
* Performance status
* Adequate organ and marrow function as defined below:
  + - leukocytes ≥ 3,000/mcL
  + - absolute neutrophil count ≥ 1,500/mcL
  + - platelets ≥ 100,000/mcl
  + - total bilirubin within normal institutional limits
  + - AST(SGOT)/ALT(SPGT) ≤ 2.5 X institutional upper limit of normal
  + - creatinine within normal institutional limits
* Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
  + A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
    - Has not undergone a hysterectomy or bilateral oophorectomy; or
    - Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).
* Other study-specific criteria
* Ability to understand and the willingness to sign a written informed consent.

## Exclusion Criteria

For example:

* Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
* Patients may not be receiving any other investigational agents.
* 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.
* History of allergic reactions attributed to compounds of similar chemical or biologic composition to Agent(s) or other agents used in study.
* Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
* Patients must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

## Accrual Goal

Define the number of subjects to be enrolled. Consider the number of subjects that you will need to enroll to get the desired number completed (assuming some attrition will occur). For example, if you need 20 subjects to complete the study, your protocol might state “Up to 30 subjects will be enrolled to ensure 20 subjects complete the study.” If UAMS will be the lead site of a multi-site study, discuss accrual goals for each site in relation to total accrual.

## Recruitment Plan

Discuss plan for recruitment of subjects. Will flyers or advertisements be distributed (if so, include as an appendix)? Will potential subjects be referred to the PI or invited to participate at routine clinic visits?

# INVESTIGATIONAL PRODUCT

## Test Article

**Agent XXX**

Provide background information and description of investigational product to include as applicable: manufacturer; other names for the product; classification/type of agent; mode of action; storage and stability; protocol dosage; formulation and packaging; route of administration for the study; availability (e.g., “commercially available”, “provided by sponsor”; specify if provided free of charge as this has implications for the consent form.); and known side effects.

### Dispensing

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

### Treatment Compliance

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

## Treatment Dosage and Administration

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

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

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **REGIMEN DESCRIPTION** | | | | | |
| **Agent** | **Premedications;**  **Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Agent X | Premedicate with DRUG for 3 days prior to Agent X. | 300 mg/m2 in  500 cc NS | IV over 2 hours **before** Agent Y | Days 1-3, week 1 | 4 weeks (28 days) |
| Agent Y | Avoid exposure to cold (food, liquids, air) for 24 hrs after each dose. | 150 mg/m2 in  250 cc D5W | IV 1 hr after completion of Agent Y; separate IV line required | Days 1-3, week 1 |
| Agent Z | Take with food. | 50 mg tablet | PO in the a.m. | Daily, wks 1 & 2 |

*For phase I dose-escalation studies*: Please state the starting dose of the study agent/drug and describe the dose escalation scheme and treatment regimen. **Use exact dose rather than percentages**. Please describe the number of patients to be treated at each level and how a decision about dose escalation or expansion of cohort sizes will be made. If there are multiple agents being used in the study, include dose escalation for each agent. Please note that escalation of only one drug at each dose level is recommended.

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

|  |  |  |
| --- | --- | --- |
| **Dose-Escalation Schedule** | | |
| **Dose Level** | **Dose of the Study Agent(s)\*** | **Minimum Number of Patients** |
| Level -1 |  | 3 |
| Level 1 |  | 3 |
| Level 2 |  | 3 |
| Level 3 |  | 3 |
| Level 4 |  | 3 |
| \*Doses are stated as exact dose in units (e.g., mg/m2, mcg/kg, etc.) rather than as a percentage | | |

Dose-Limiting Toxicity (DLT) and Maximally Tolerated Dose (MTD):

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

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

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

## Toxicities and Dosing Delays/Dose Modifications

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

Treatment plans should explicitly identify when treatment (typically dosage) modifications are appropriate. Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear. For phase I studies, there should be consistency between toxicities which mandate dose reductions, and those events which are considered a DLT. If dose modifications or treatment delays are anticipated, please provide a dose de-escalation schema. If there are multiple agents being used in the study, provide a detailed description of toxicity grades and method of dose modification for each agent separately. In the event that more than one study agent could be responsible for a given toxicity, please address in what order each agent should be modified/delayed and provide justification (if available). You may also want to refer reader to the appropriate section in the protocol that contains more detailed information on the potential adverse events and risks associated with each agent (either in Section 1.2,1.3 or Section 8.0). All treatment modifications should be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose. Please also address how many missed days of treatment or missed cycles warrants removal of the patient from the study. If patients may remain on study after missed days or cycles, please specify when treatment under study may resume.

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

Example 1 Hematological Toxicities

|  |  |  |
| --- | --- | --- |
| **Hematological Toxicity Dose Reductions for Agent A** | | |
| **ANC1** | **Platelets** | **Action** |
| ≥ 1,500/μL | 100,000/μL | None. |
| 1000-1499/μL | 75,000-99,000/μL | *-1st Occurrence:* Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose.  *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose.  *-3rd Occurrence:* Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose.  *-4th Occurrence*: Discontinue protocol therapy. |
| 500-999/μL | 50,000-74,000/μL | *-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose.  -*2nd Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose.  *-3rd Occurrence*: Discontinue protocol therapy. |
| <500/μL | <50,000/μL | *-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Restart next treatment at TBD dose.  *-2nd Occurrence*: Discontinue protocol therapy. |
| 1Note: G-CSF (Filgrastim) may be added for low ANC on day of treatment *BEFORE* a dose reduction is instituted at treating physician’s discretions. Neulasta® is NOT allowed. | | |

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

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

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

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

## Concomitant Medications/Treatments

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

## Other Modalities or Procedures

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

## Duration of Therapy

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

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

## Duration of Follow Up

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

## Removal of Patients from Protocol Therapy

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

## Patient Replacement

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

# STUDY PROCEDURES

## Screening/Baseline Procedures

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

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

### *Informed Consent*

### *Medical history*

Complete medical and surgical history, history of infections

### *Demographics*

Age, gender, race, ethnicity

### *Review subject eligibility criteria*

### *Review previous and concomitant medications*

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

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

### *Performance status*

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

### *Adverse event assessment*

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

### *Hematology*

### *Blood draw for correlative studies*

See Section 9.0 for details.

### *Serum chemistries*

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

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

See section 3.1.6.1 for definition.

### *Tumor assessment*

To be performed…

### *Other*

Describe…

## Procedures During Treatment

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

### Prior to Each Treatment Cycle

* Physical exam, vital signs
* Hematology
* Serum chemistries

### Day 1

* Procedure

### 30 days after treatment termination

* Physical exam, vital signs
* Hematology
* Serum chemistries

## Follow-up Procedures

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

* Procedure

## Schedule of Time and Events Table

Please see the example below; list the specific day or days if appropriate, e.g., Day 1, Cycle 1 or Days 1, 7… etc.). Please ensure table reconciles with study objectives, eligibility criteria, and assessments in sections 8.1-8.3.\*

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

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

## Removal of Subjects from Study

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

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

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

5.5.3 Patient is unable to comply with protocol requirements;

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

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

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

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

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

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

# Outcome Measures

Provide a description of the outcome measures and endpoints to be used to evaluate efficacy of the study intervention. See examples below.

## Antitumor Effect- Solid Tumors

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

If using RECIST, state:

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

### Definitions

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

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

If using RECIST, state:

### Disease Parameters

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

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

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

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

### Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

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

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

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

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

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

### Response Criteria

#### Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

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

#### Evaluation of Non-Target Lesions

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

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

#### Evaluation of Best Overall Response

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Response for this Category Also Requires:** |
| CR | CR | No | CR | >4 wks. confirmation |
| CR | Non-CR/Non-PD | No | PR | >4 wks. confirmation |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD | documented at least once >4 wks. from baseline |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD\* | Yes or No | PD |
| Any | Any | Yes | PD |
| \* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.  Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration”*. Every effort should be made to document the objective progression even after discontinuation of treatment. | | | | |

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

### Duration of Response

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

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

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

### Progression-Free Survival

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

## Antitumor Effect- Hematologic Tumors

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

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

### Primary Efficacy/ Response assessment - clinical response following 3 cycles of treatment. If patient is clinically in CR (without or with cytopenias) peripheral blood should be assessed for clonal lymphocytes.

### Final Response Assessment- Will occur two months following completion of treatment with sorafenib. It is acknowledged that to meet iwCLL Guidelines for response in CLL, a response assessment must be performed 2 months from therapy to document responses including a bone marrow to confirm CR and a CT maybe indicated or recommended. Therefore, those patients that clinically appear to be in CR will have a bone marrow and possibly a CT scan to confirm complete responses at least 3 months after all treatment.

## Safety/tolerability

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

# ADVERSE EVENTS

## Experimental Therapy

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

### Contraindications

### Special Warnings and Precautions for Use

### Interaction with other medications

### Adverse Reactions

## Adverse Event Monitoring

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

## Definitions

### Definition of Adverse Event

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

### Severity of Adverse Events

Cancer-related trials should grade AEs according to the most current version of the CTCAE: All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at <http://ctep.cancer.gov/reporting/ctc.html>

If trial is not cancer-related: The severity of adverse events will be graded as follows (or replace with your own study-specific severity classification scale):

Mild: the event causes discomfort without disruption of normal daily activities.

Moderate: the event causes discomfort that affects normal daily activities.

Severe: the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

### Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that meets one or more of the following criteria:

#### Results in death.

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

#### 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

#### Is an important medical event

#### Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

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

## Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the adverse event.

Step 2: Determine whether the adverse event is related to the protocol therapy.

Attribution categories are as follows:

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

Step 3: Determine the prior experience of the adverse event.

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

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

Step 4: Determine whether the adverse event is a Serious Adverse Event

## Reporting Requirements for Adverse Events

### Expedited Reporting

* The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study.
  + - If applicable, insert terms for expedited reporting to the pharmaceutical company/entity if they are providing funding and require expedited reporting.
    - The IRB must be notified within 10 business days of any unanticipated problems involving risk to subjects or others” (UPIRTSO). A UPIRTSO is defined as any problem, event or new information that is:

1. Unanticipated or unexpected;
2. Related to the research; and
3. Involves new or increased risks to subjects or others.
   * + For IND/IDE trials: The FDA should be notified within 7 business days of the Sponsor learning of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of the Sponsor learning of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

### Routine Reporting

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

## Unblinding Procedures

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

## Stopping Rules

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

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

# CORRELATIVES/SPECIAL STUDIES

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

## Sample Collection Guidelines

What kind samples will be collected using what. Samples will be labeled with the subject’s de-identified study number and collection date and delivered for analysis to:

<Insert Location/Address>

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

Samples will be collected at the following time points (+/- window):

* (Within 28 days) prior to study treatment.
* ETC…

## Assay Methodology

## Specimen Banking

<if applicable>

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

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

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UAMS, the investigator or a collaborating researcher or entity.

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

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

# STATISTICAL CONSIDERATIONS

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

## Study Design/Study Endpoints

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

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

## Sample Size and Accrual

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

## Data Analyses Plans

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

# STUDY MANAGEMENT

## Institutional Review Board (IRB) Approval and Consent

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures.  This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB).

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure.  All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study.  The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study.  The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation.  Participation privacy will be maintained and questions regarding participation will be answered.  No coercion or undue influence will be used in the consent process.  This consent form must be signed by the subject or legally acceptable surrogate, and the individual obtaining the consent.  A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject’s research record.

## Data Management and Monitoring/Auditing

Describe data management methods including measures to protect subject confidentiality (i.e., coding of data, data storage, security measures, etc.) Describe QA activities, monitoring committee(s), etc. For multi-site studies, describe management of data across study sites.

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

## Amendments to the Protocol

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

The amended protocol, and if required the amended consent form, must be approved by the IRB (and submitted to the FDA when applicable) prior to implementation.

## Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). All study records will be retained in accordance with applicable institutional and applicable regulatory requirements.

## Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with applicable regulatory requirements. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

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

# REFERENCES

List all protocol references.

# APPENDICES

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

Example: An appendix for a Drug Diary may be included for self-administered investigational agents.