**INSTRUCTIONS**

* You must submit the **Biomedical protocol checklist** with your protocol, to attest that you have considered all the required sections in this template.
* If unsure whether IRB review is required for your project, please start by using our website tool at <http://irb.emory.edu/forms/review/index.html>: “Does My Project Need IRB Review?”
* Please use this outline for studies with a biomedical component that involve subject intervention, for studies involving solely a review of medical charts, please see “Retrospective Chart Review Protocol Outline” on emory IRB website instead.
* Grant applications normally may **not** be submitted to the IRB in lieu of a protocol document.
* Depending on the nature of your study, some sections may not be applicable to your research. If so, mark as “NA.”.
* As you are writing the protocol, remove all instructions so that they are not contained in the final version of your protocol.
* Depending on the phase of the study and whether it is a single-agent or combination agent study, sections are highlighted to assist with your protocol development:

Grey Highlight italics - General Instructions

**Green** –**phase 1 protocols**

**Magenta** – **Multi-site protocols**

****

**PROTOCOL TITLE:**

**WINSHIP PROTOCOL #:**

**COORDINATING CENTER:** *Name of Organization (If this is a multi-institution study, only one organization/institution can be the coordinating center).*

**PRINCIPAL INVESTIGATOR:**

Name

Department

Telephone Number

Email Address

**CO-INVESTIGATORS:**

Name
Address
Telephone
e-mail address

**STATISTICIAN:**

Name
Address
Telephone
e-mail address

**MULTISITE CONTACT: Winship Multisite Coordinator**

**EXTERNAL (NON-EMORY) COLLABORATORS**

Name, Title(s), Institution, and Department of External Collaborators
(For each entry, please indicate whether that institution’s IRB will review (or has already reviewed) that individual’s engagement in human participants research activities)

**VERSION:** Include the version number and date of this protocol. (Version #; mm/dd/yyyy)

**FUNDING SOURCE:** *Include the information for the funding entity for this study. Please explain if this study is covered by a sub-award or other pertinent information. Say “department” if you do not have any other funding.*

**INVESTIGATIONAL PRODUCT (IP)**: [*Agent Name and Supplier*]

**OTHER AGENT(S):** [*Agent Name and Supplier*]

**IND # :**

**☐ Study Exempt from IND Requirements per 21 CFR 312.2(b).**

**REVISION HISTORY**

|  |  |  |
| --- | --- | --- |
| **Revision #** | **Version Date** | **Summary of Changes** |
|  |  |  |
|  |  |  |

Table of Contents

[1. Study Summary 4](#_Toc39065592)

[1.1 Synopsys 4](#_Toc39065593)

[1.2 Schema 5](#_Toc39065594)

[1.3 Schedule of Assessments 6](#_Toc39065595)

[2. Objectives (and Endpoints) 7](#_Toc39065596)

[3. Background 8](#_Toc39065597)

[3.1 Study Rationale 8](#_Toc39065598)

[3.2 Clinical Experience 8](#_Toc39065599)

[4. Study Intervention/Investigational Agent 9](#_Toc39065601)

[4.1 Description 9](#_Toc39065602)

[4.2 Drug/Device Handling 9](#_Toc39065603)

[4.3 Accountability 9](#_Toc39065604)

[5. Procedures Involved 10](#_Toc39065605)

[5.1 Study Design 11](#_Toc39065606)

[5.2 Dosing and Administration 11](#_Toc39065607)

[5.3 Definition of Dose-Limiting Toxicity 13](#_Toc39065608)

[5.4 Dose Modification 14](#_Toc39065609)

[5.5 Concomitant medication 15](#_Toc39065610)

[5.6 Study Procedures 15](#_Toc39065611)

[5.7 Description of Study Procedures 17](#_Toc39065612)

[6. Data and Specimen Banking 18](#_Toc39065613)

[7. Sharing of Results with Participants 19](#_Toc39065614)

[8. Study Timelines 19](#_Toc39065615)

[8.1 Duration of therapy 20](#_Toc39065616)

[8.2 Duration of follow-up 20](#_Toc39065617)

[9. Inclusion and Exclusion Criteria 21](#_Toc39065618)

[10. Vulnerable Populations 22](#_Toc39065619)

[11. Local Number of Participants 23](#_Toc39065620)

[12. Recruitment Methods 23](#_Toc39065621)

[13. Withdrawal of Participants 25](#_Toc39065622)

[14. Risks to Participants 25](#_Toc39065623)

[15. Potential Benefits to Participants 26](#_Toc39065624)

[16. Data Management and Confidentiality 26](#_Toc39065625)

[16.1 Statistical consideration section: Biostatistician 26](#_Toc39065626)

[16.2 Data/specimens: 26](#_Toc39065627)

[17. Provisions to Monitor the Data to Ensure the Safety of Participants 27](#_Toc39065629)

[18. Provisions to Protect the Privacy Interests of Participants 36](#_Toc39065630)

[19. Economic Burden to Participants 37](#_Toc39065631)

[20. Consent Process 37](#_Toc39065632)

[21. Setting 40](#_Toc39065633)

[22. Resources Available 41](#_Toc39065634)

[23. Multi-Site Research when Emory is the Lead Site 42](#_Toc39065635)

[24. References 44](#_Toc39065636)

[APPENDIX A PERFORMANCE STATUS CRITERIA 44](#_Toc39065637)

[APPENDIX B Drug Diary 46](#_Toc39065638)

[APPENDIX C Abbreviations and definition of terms 47](#_Toc39065639)

# Study Summary

1.1 Synopsys

|  |  |
| --- | --- |
| **Title:** | *Full title* |
| **Study Description:** |  *Provide a short description of the protocol, including a brief statement of the study hypothesis.****Ex.***This research study is an open label, single arm, Phase II study, designed to evaluate the safety and tolerability/efficacy of the combination **Study drugs** in subjects with previously-untreated/metastatic **CANCER TYPE**.  |
| **Objectives:** | *Include the primary and secondary objectives.****Ex.*****Primary Objective**: To evaluate the anti-tumor activity of the combination of **STUDY DRUGS** by assessing the Overall Response Rate (ORR)/PFS/OS by RECIST 1.1.**Secondary Objectives:*** To evaluate the safety and tolerability of the combination of **STUDY DRUGS** in patients with **CANCER TYPE**.

**Exploratory Objective:*** To evaluate the effect of treatment on selected biomarkers in the tumor microenvironment and systemic circulation.
 |
| **Endpoints:** |  *Include the primary endpoint and secondary endpoints.****Ex.*** **Primary Endpoint:** * Efficacy

ORR per RECIST 1.1 (Tumor measurements will be performed at **X** weeks)**Secondary Endpoints:** * Safety: adverse events, vital sign measurements, physical examinations, and clinical laboratory test.
* Efficacy: Progression Free survival (PFS) and Overall Survival (OS)
* Exploratory: Changes in selected biomarkers in tumor microenvironment and circulation before and after treatment with **STUDY DRUGS.**
 |
| **Study Population:** | *Specify the sample size, gender, age, demographic group etc.****Ex.***The patient population consists of subjects ≥18 years of age with. Eligible patients must have/have not (Specifics). |
| **Phase:** | Phase I/II/III; Feasibility/Pilot |
| **Description of Sites/Facilities Enrolling Participants:** | *Provide a brief description of planned facilities/participating sites enrolling participants:****Ex.*** Winship Cancer Institute of Emory University (Atlanta, GA). |
| **Description of Study Intervention:** | *Describe the study intervention. If the study intervention is a drug or biologic, include dose and route of administration.****Ex.***Patients will receive the following treatment: study drug (X mcg IV/ PO) twice weekly/ daily. Study drugs will be given IV/PO on Days X for X Cycles. Treatment cycles are X weeks. |
| **Study Duration:** | *Estimated time (in months) from when the study opens to enrollment until completion of data analyses.****Ex.***Patients will be treated until unacceptable toxicity, death, or disease progression per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1). |

1.2 Schema

***Example #1 Timeline diagram*** *(e.g., randomized controlled trial):*

Day -7 to Day -1

Screening

Day 1

Randomization

Week 1

Titration

Weeks 2 - 25

Maintenance

Week 26

Dose Taper

Week 27

End of Study Assessments (EOS)

Week 28-29

Follow-up Phone Call

Study Intervention N=

Placebo N=

# in-clinic visits

***Example # 2 provided as a guide for dose escalation stuies, customize as needed: For phase 1 single-agent protocols:***

|  |
| --- |
| **Dose Escalation Schedule** |
| **Dose Level** | Dose of [IND Agent]\* |
| Level 1 |  |
| Level 2 |  |
| Level 3 |  |
| *\* Doses are stated as exact dose in units (*e.g.*, mg/m2, mcg/kg, etc.) rather than as a percentage.* |

1.3 Schedule of Assessments

| **Procedures** | **Screening**Day -7 to -1 | **Enrollment/Baseline**Visit 1, Day 1 | **Study Visit 2** Day 7 +/-1 day | **Study Visit 3**Day 14 +/- 1 day | **Study Visit 4**Day 21 +/-1 day | **Study Visit 5**Day 28 +/-1 day | **Study Visit 6**Day 35 +/-1 day | **Study Visit 7**Day 42 +/-1 day | **Study Visit 8**Day 49 +/-1 day | **Study Visit 9**Day 56 +/-1 day | **Study Visit 10**Day 63 +/-1 day | **Study Visit 11**Day 70 +/- 1 day | **Study Visit 12**Day 77 +/-1day | **Final Study Visit 13**Day 84 +/-1 day  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Randomization | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Administer study intervention |  | X |  |  | X |  |  | X |  |  | X |  |  |  |
| Con. medication review | X | X---------------------------------------------------------------------------------------------X |  |
| Physical exam (including height and weight) | X | X |  |  | X |  |  | X |  |  | X |  |  | X |
| Vital signs | X | X |  |  | X |  |  | X |  |  | X |  |  | X |
| Height | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Weight | X | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Performance status | X | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Hematology  | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| serum chemistry a | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test b | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EKG (as indicated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| AEs review and evaluation | X | X---------------------------------------------------------------------------------------------X | X |
| Radiologic/Imaging assessment | X |  |  |  | X |  |  |  | X |  |  |  |  | X |
| Other assessments (e.g., immunology assays, pharmacokinetic) | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete Case Report Forms (CRFs) | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.b: Serum pregnancy test (women of childbearing potential). |

# Objectives (and Endpoints)

Describe the purpose, specific aims, or objectives and state the hypotheses to be tested.

| OBJECTIVES | ENDPOINTS |
| --- | --- |
| Primary |  |
| 1. To evaluate the safety and tolerability of STUDY DRUG in combination with STUDY DRUG in patients with **X** cancer.
2. To evaluate anti-tumor activity of the combination of STUDY DRUGS by assessing the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST 1.1).
 | * Safety: adverse events, vital sign, ECG, physical examinations, clinical laboratory test.
* Efficacy:
* ORR per RECIST 1.1 (Tumor measurements will be performed every **X** weeks ± **X** days
 |
| Secondary |  |
| * To evaluate the efficacy of the combination of STUDY DRUGS by assessing ORR by immune-related RECIST (irRECIST).
* To evaluate the anti-tumor activity of the combination of STUDY DRUGS by assessing progression-free survival (PFS) and overall survival (OS)
 | * ORR per irRECIST
* Progression-free Survival (PFS) using RECIST 1.1
* Overall Survival
 |
| Tertiary/Exploratory  |  |
| * To assess the effects of the combination of STUDY DRUGS on immune cells in blood and tumor.
* To assess the association between efficacy measures and X expression in tumors.

To assess the association between anti-tumor activity and immune cells in tumor and blood. | * Changes in immune system biomarkers after treatment STUDY DRUGS and their relationship with efficacy.
 |

# Background

Describe the relevant prior experience and gaps in current knowledge.

Provide the scientific background for your research study based on the existing literature.

3.1 Study Rationale

*Provide the scientific rationale for, and significance of the research and how will it add to existing knowledge.*

3.2 Clinical Experience

*Describe any relevant preliminary data.*

# Study Intervention/Investigational Agent

4.1 Description

*Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated. Product information can usually be obtained from the IB or Package Insert.*

4.2 Drug/Device Handling

If the research involves drugs or device, describe your plans **to store, handle, and administer** those drugs or devices so that they will be used only on participants and be used only by authorized investigators.

* If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., IDS SOP, VA Research Pharmacy, CHOA pharmacy, Grady Pharmacy, etc.).
	+ - If the drug is under an FDA [REMS](https://www.fda.gov/AboutFDA/Transparency/Basics/ucm325201.htm) . Please also plan to complete the [REMS checklist](http://irb.emory.edu/documents/REMS_checklist.docx) found here, on the IRB website.
		- If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:
		- Identify the holder of the IND/IDE/Abbreviated IDE. An Emory investigator who holds an IND or IDE is considered to be a Sponsor-Investigator. If this applies for this study, please review the guidance found at <http://irb.emory.edu/documents/guidance-EmorySI.pdf>.
		- Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:

|  |  |
| --- | --- |
|  | **Applicable to:** |
| **FDA Regulation** | **IND Studies** | **IDE studies** | **Abbreviated IDE studies** |
| **21 CFR 11** | **X** | **X** |  |
| **21 CFR 54** | **X** | **X** |  |
| **21 CFR 210** | **X** |  |  |
| **21 CFR 211** | **X** |  |  |
| **21 CFR 312** | **X** |  |  |
| **21 CFR 812** |  | **X** | **X** |
| **21 CFR 820** |  | **X** |  |

4.3 Accountability

*NOTE: For orally administered agents, a method for assessing compliance with treatment should be included, i.e.,*

“The patient will be requested to maintain a medication diary of each dose of medication. The medication diary (AppendixE) will be returned to clinic staff at the end of each cycle.

**Example:**

The study drug provided for this study will be used only as directed in the study protocol. The Winship IDS (Investigational Drug Service) personnel will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.

Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.

The Drug Accountability Log may record specifics to study drug dispensation such as:

• Records of product delivery, inventory, temperature monitoring, destruction, and return.

• Dosages prepared, time prepared, doses dispensed.

• Doses and/or vials destroyed.

• The Drug Accountability Log will be reviewed by the monitor during site visits and at the completion of the study.

Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

The study drug supply will be disposed of as per Winship’s Investigational Pharmacy (IDS) SOP

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

# Procedures Involved

Describe and explain the study design and include a study schema, if possible.

Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor participants for safety or minimize risks.

Describe:

Procedures performed to lessen the probability or magnitude of risks.

All drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

The source records that will be used to collect data about participants. (Attach all surveys, scripts, and data collection forms.)

What data will be collected during the study and how that data will be obtained.

If there are plans for long-term follow-up (once all research related procedures are complete), what data will be collected during this period.

**Example:**

5.1 Study Design

This clinical trial is a Phase 1b-2 study of the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and antitumor activity of the combination of *(study drugs)*.

**Dose-Finding:** Part 1 comprises a Phase 1b, open-label, sequential allocation, dose-finding evaluation of the sequential administration of STUDY DRUG monotherapy followed by combination therapy in subjects with (cancer type) who have not received prior inhibitor therapy. Subjects will be administered study therapy as follows:

**Cohort Expansion**: Part 2 comprises a Phase 1b, open-label evaluation of the concurrent administration of STUDY DRUG based on the RDR derived from Part 1. Six evaluable subjects with each disease type and who have not received prior inhibitor therapy will be accrued. Subjects will be administered study therapy as follows:

**Efficacy Evaluation:** Part 3 comprises a Phase 2 open-label, randomized, controlled 2-arm, parallel-group evaluation of the clinical activity and safety of combination therapy versus *(DRUG)* alone. Subjects with (cancer type) who have not received prior inhibitor therapy will be randomized 2:1 to one of the following 2 regimens in blocks of 6 subjects using a pre-generated randomization list:

The study is divided into a Screening period, Treatment period, End of Treatment (EOT) period, and Follow-up period.

During Screening period patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient’s standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam) as long as the procedures were completed within the **28-day screening period**. After signing the ICF, patients will be evaluated for entry criteria during the screening period within 28 days before administration of study drug(s). Rescreening after screen failure will be allowed.

Subjects with (cancer type) will be assigned one of the following 2 arms:

ARM A

ARM B

Treatment will continue until unacceptable toxicity, death, disease progression per RECIST 1.1, Investigator’s decision to discontinue treatment, the patient withdraws consent, is lost to follow-up, or Institution decides to terminate the trial.

Patients with PD per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section “Treatment beyond progression”. Patients with a PR or SD will continue to receive treatment until achievement of a confirmed complete response (CR), disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating patients with a confirmed CR.

5.2 Dosing and Administration

*For phase 1 dose-escalation protocols: State the starting dose of each agent and describe the dose escalation scheme and treatment regimen.*

|  |
| --- |
| **Dose Escalation Schedule** |
| **Dose Level** | Dose of *[ IND Agent]\** |
| Level 1 |  |
| Level 2 |  |
| *\* Doses are stated as exact dose in units (*e.g.*, mg/m2, mcg/kg, etc.) rather than as a percentage.* |

|  |
| --- |
| **Regimen Description** |
| **Agent** | **Premedications; Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| [Agent X] | Premedicate with dexamethasone for 3 days prior to [Agent X] | in 500 cc NS | IV over 2 hours **before** [Agent Y] | Days 1-3, week 1 | *28 days**(4 weeks)* |
| [Agent Y] | Avoid exposure to cold (food, liquids, air) for 24 hr after each dose. | in 250 cc D5W | IV 1 hr after completion of Agent A through separate IV line | Days 1-3, week 1 |
| [Agent Z] | Take with food. | tablet | PO in the a.m.  | Daily, weeks 1 and 2 |

**Dose escalation**:

Cohorts will be enrolled sequentially and will follow a 3+3 design: at dose Level1 , 3 patients will be enrolled and if there are no Dose Limiting Toxicities (DLTs) (see DLT criteria below) observed in any of the 3 patients through the DLT observation period (i.e., through Cycle 1/Day 28), then the next higher Dose Level cohort will open for enrollment. If 1 of the first 3 patients experiences a DLT, then 3 additional patients will be enrolled (total of 6 evaluable patients at the same Dose Level).

Patient will be considered evaluable for dose escalation decision if the patient has received at least **X** infusion of (agent) and had safety assessments for a minimum of **X** weeks or have had a DLT during the first **X** weeks.

Dose escalation will continue until either the MTD is reached or no more than 1 of 6 patients treated at the highest dose level experienced DLT. If ≥2 patients experienced DLT on dose level 2, then dose de-escalation will occur (dose level 1), with 6 additional patients will be enrolled at this dose level.

Inpatient dose escalation will not be permitted. Patients who receive less than 75% of intended dose due to compliance (not toxicity) will be considered unevaluable for phase I portion and will be replaced.

The PI or designee must obtain approval from the DSMC for dose escalation. The PI will provide an update on all relevant safety data of patients entered to a dose level to the DSMC when dose escalation is planned. Upon receiving DSMC approval Letter, dose escalation will occur.

**Dose Expansion Phase**

The purpose of cohort expansion is to gather additional safety and tolerability information, and evaluate the efficacy of the (Study Agent).

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in cohort expansions, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk: benefit ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level, or at a dose level intermediate to previously tested lower dose levels.

5.3 Definition of Dose-Limiting Toxicity

*Please provide explicit definitions of the type(s), grade(s), and duration(s) of adverse events that will be considered dose-limiting toxicity (ies), or provide definitions of other endpoints that will be used to determine dose escalations.*

**Example:**

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as definitely treatment related that occurs within the first **X** weeks and meets any of the criteria included in below. National Cancer Institute Common Terminology Criteria for Adverse events version 5.0 (NCI CTCAE v. 5.0) will be used for all grading. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

**Criteria for defining dose-limiting toxicities**

**Blood and lymphatic system disorders**

1. Thrombocytopenia Grade 3 with clinically significant bleeding
2. Thrombocytopenia Grade 4
3. Neutropenia Grade 4 lasting more than 8 days
4. Febrile neutropenia CTCAE Grade ≥ 3

**Gastrointestinal disorders**

1. Diarrhea CTCAE Grade ≥ 3 ≥ 72 hrs., despite the use of anti-diarrhea therapy
2. Nausea/ vomiting CTCAE Grade ≥ 3 ≥ 72 hrs., despite the use of anti-emetic therapy

**Pneumonitis (interstitial lung disease)**

1. CTCAE Grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids.
2. Grade 3-4 pneumonitis of any duration

**Immune-related toxicities (except pneumonitis)**

* CTCAE Grade 3 immune-related toxicities that persist > 14 days with same severity despite treatment with corticosteroids.
* Immune-related toxicities CTCAE Grade 4 of any duration Other Adverse Events
* Grade 3-4 infusion reaction
* Other non-hematologic treatment-related toxicity at Grade 3 or higher

Management and dose modifications associated with the above adverse events are outlined in Section 7.1.4.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

*For Participating Sites: DLTs are to be reported to the Sponsor- Investigator within 48 hours of determination via the Reportable Event Form.*

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

5.4 Dose Modification

The investigator will decide whether any AE that occurs is related to either or both drugs and determine whether dose modification or discontinuation of one or both drugs is required per the guidance below.

**Ex.:**

Prior to each infusion, premedicate all patients with an intravenous

Reduce dose, withhold dose, or discontinue STUDY DRUG to manage adverse reactions as described in Table below and are based on criteria in the package insert.

**Table**: Dose Modification for Adverse Events Associated with STUDY DRUG

|  |  |
| --- | --- |
| **Adverse Event** | **Dose Modification** |
| Infusion-related reactions | * Reduce infusion rate by 50% for grade 1 or 2
* Permanently discontinue for grade 3 or 4
 |
| Hypertension | * Interrupt infusion for severe hypertension until controlled with medical management
* Permanently discontinue if severe hypertension cannot be controlled with antihypertensive therapy
 |
| Proteinuria | * Interrupt ramucirumab for urine protein levels ≥2g/24h (first occurrence). Reinitiate treatment at a reduced dose of 8 mg/Kg every 3 weeks once the protein level returns to <2g/24h.
* If the urine protein level ≥2g/24h reoccurs, interrupt ramucirumab and reduce the dose to 6 mg/Kg every 3 weeks once the urine protein level returns to <2g/24h.
* Permanently discontinue if urine protein levels >3g/24h or in the setting of nephrotic syndrome.
 |
| Wound healing complications (all grades) | Withhold ramucirumab for 28 days prior to elective surgery. Resume ramucirumab no sooner than 28 days after surgery and until the surgical wound is fully healed. Discontinue ramucirumab for wound healing complications that require medical intervention.  |
| Arterial thromboembolic events (all grades) | Permanently discontinue ramucirumab |
| Gastrointestinal perforation (all grades) | Permanently discontinue ramucirumab |
| Grade 3 or 4 bleeding | Permanently discontinue ramucirumab |
| Reversible posterior leukoencephalopathy syndrome | Permanently discontinue ramucirumab for confirmed diagnosis |

5.5 Concomitant medication

**Example**

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required

*List Acceptable Medication and Prohibited concomitant medications.*

5.6 Study Procedures

**Example:**

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis*.*

### Screening Phase

Screening procedures will be performed up to 14 days prior to randomization and initiation of radiation therapy as applicable, except for baseline imaging (up to 28 days allowed) unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Visit**:

* Informed Consent
* Review of eligibility criteria
* Randomization
* Medical history and demographics
* Complete physical exam
* ECOG Performance Status
* Vitals signs, weight and height
* 12-lead ECG
* Tumor biopsy
* Review of prior/concomitant medications
* Imaging by CT/MRI
* Clinical laboratory tests for:
* Hematology
* Clinical chemistry
* TSH
* Coagulation (PT, PTT, INR)
* Creatinine Clearance
* Serum or urine pregnancy test (for women of childbearing potential)
* Hepatitis serologies
* Urinalysis

### Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3). Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

* Brief medical history
* Symptom-directed physical exam
* ECOG Performance Status
* Vitals signs, weight
* 12-lead ECG
* Review of prior/concomitant medications
* Clinical laboratory tests for:
1. Hematology
2. Clinical chemistry
3. TSH
4. Serum pregnancy test (for women of childbearing potential)
5. Hepatitis serologies (if clinically indicated)
6. Urinalysis (see Table 8)
* Arm I: Drug Treatment description
* Arm II: Drug Treatment description

**End of Treatment**

* End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue drug treatment prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.
* Assessments for subjects who have completed treatment and achieved disease control, or have discontinued treatment due to toxicity in the absence of confirmed progressive disease are provided in the Schedule of Event.
* All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

5.7 Description of Study Procedures

### Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

### Physical examination

Physical examinations should be conducted according to the Schedule of Events. Full physical examinations should be conducted at screening/baseline, Day 1 of cycle 2 and beyond, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient’s clinical symptoms. Weight is to be reported at each visit, height at screening/baseline visit only.

**Vital signs**

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.

On infusion days, patients receiving treatment will be monitored during and after infusion of IP as presented in the bulleted list below.

* Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):
* Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]).
* Approximately 30 minutes during the infusion (**halfway** through infusion).
* At the end of the infusion (approximately 60 minutes ±5 minutes).
* A 1-hour observation period is required after the first infusion. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator’s discretion (suggested 30 minutes after each infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

### Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At Screening, a single ECG will be obtained on which QTcF must be <450 ms.

In case of clinically significant ECG abnormalities, including a QTcF value >450 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE.

**Echocardiograms**

An echocardiogram will be performed for all patients within 60 days prior to C1D1 and at EOT to assess cardiac function and left ventricular ejection fraction (LVEF). The same assessment method should be used for the same patient throughout the study.

### Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

* Hematology and Clinical Chemistry
* Urinalysis
* Coagulation parameters: Activated partial thromboplastin timeand International normalised ratioto be assessed at baseline and as clinically indicated
* Pregnancy test (female subjects of childbearing potential only)
* Thyroid Stimulating Hormone
	+ free T3 and free T4 only if TSH is abnormal
* Other laboratory tests
	+ Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
	+ HIV antibody

# Data and Specimen Banking

If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens. (may require a separate repository-specific IRB submission). The VA Data Repository SOP is required if the study is creating a data repository at the Atlanta VA

List the data to be stored or associated with each specimen.

Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

**Example:**

**Blood (tumor, bone marrow etc.) samples** will be obtained and used for medical research by the investigators of this study. Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify participants will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.

Samples and data collected under this protocol may be used to study **Cancer Type**. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in subject’s medical record. For this study, those items include: research blood collection.

Correlative peripheral blood samples will be collected prior to study drug allotment, to assess STUDY DRUG pharmacokinetics.

# Sharing of Results with Participants

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with participants or others (e.g., the participant’s primary care physicians) and if so, describe how the results will be shared If applicable (e.g. for studies involving scans and/or panels of exploratory testing on specimens)

Plan for managing the types of findings that might arise. This should include any secondary findings that are being sought actively, findings that might be anticipatable, and findings that might be un-anticipatable.

Plan for recognizing, analyzing, and handling incidental findings and how incidental findings will be communicated to participants during the consent process. If the plan is not to disclose any findings, then this should be included. This plan might include the option for participants to opt out of receiving incidental findings.

Description of the research team’s responsibilities following disclosure of a finding. This should detail educational information about the nature of the finding, how to seek care from a clinician or specialist, obtaining health insurance to secure treatment, and/or referral to a clinical specialist, if one is required.

Reminder to include language in the consent form to let the participants know your plans for this – see Modular Language for Informed Consent Forms on IRB website)

**Example:**

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject’s samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

# Study Timelines

Describe:

* The duration of an individual participant’s participation in the study.
* The duration anticipated to enroll all study participants.
* The estimated date for the investigators to complete this study (complete primary analyses)

**Example:**

8.1 Duration of therapy

In the absence of treatment delays due to adverse event(s), patients will be treated until any one of the following:

• Tumor progression per RECIST 1.1

• Death

• Unacceptable toxicity

• Symptomatic deterioration

• Achievement of maximal response

• Investigator’s decision to discontinue treatment

• Patient decision to discontinue treatment

• Patient withdraws consent

• Lost to follow up

In the event of a patient’s withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events.

8.2 Duration of follow-up

Patients will be followed for approximately X days (Safety Follow-up) after the last dose of study drug or before initiation of new antineoplastic or investigational therapywhichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Long-term follow-up should continue until the patient’s withdrawal of consent or loss to follow up, death, or study termination.

Patient records may be reviewed until death to assess progression and survival. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

• All patients will be contacted for survival every X weeks following the End of Treatment (EOT) visit.

• Immunogenicity samples will be taken as per schedule of events

Patients who have not initiated a new antineoplastic regimen will have the following assessments:

 • Radiologic tumor assessments every X weeks (± 7 days)

 • In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

# Inclusion and Exclusion Criteria

Describe how individuals will be screened for eligibility.

Describe the criteria that define who will be included or excluded in your final study sample.

Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the above populations as participants in your research unless you indicate this in your inclusion criteria.)

* Adults unable to consent
* Individuals who are not yet adults (infants, children, teenagers)
* Pregnant women,
* Prisoners

*Community Participation: For studies aimed at addressing issues that affect a certain community or group: How, if at all, will this study involve people from the target community in the design of the study? Conduct of the study? How will the results of the research be shared with the participants and/or the target community/ies?*

**Example**

**Inclusion Criteria**

1. Age ≥18 years.
2. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
3. Life expectancy > 12 weeks as determined by the Investigator
4. Patients must have adequate organ and marrow function, within 28 days of Cycle 1 Day 1, as defined below:

**Hematology**

Hemoglobin ≥ 9.0 g/dl (no transfusions allowed within 7 days of Cycle 1 Day 1 to meet entry criteria)

White blood cell (WBC) ≥ 2000/μL (after at least 7 days without growth factor support or transfusion)

Absolute neutrophil count (ANC) ≥ 1,500/mcL (after at least 7 days without growth factor support or transfusion)

Platelets ≥ 100,000/mcL (no transfusions allowed within 7 days of Cycle 1 Day 1 to meet entry criteria)

PT/PTT ≤ 1.5 x ULN

**Chemistry**

Total bilirubin ≤2 institutional upper limit of normal (ULN)

 AST/ALT ≤ 3 institutional upper limit of normal (ULN)

Serum creatinine ≤ 2 mg/dL (or glomerular filtration rate ≥ 40 mL/min)

Lipase and Amilase ≤ 1.5× ULN (< 3× ULN if subject with pancreatic metastases)

**Cardiac**

Electrocardiogram QTcF <450 ms (average of 3 readings approximately 2 minutes apart)

Echocardiogram documented left ventricular ejection fraction > 45% within 60 days prior to C1 Day 1

1. The effects of *[IND Agent]* on the developing human fetus are unknown. For this reason and because *[Agent Class]* as well as other therapeutic agents used in this trial are known to be teratogenic, female of child-bearing potential (FCBP) must have a negative serum or urine pregnancy test prior to starting therapy.
2. FCBP and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and X months after completion of *[IND Agent]* administration. A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.
3. Completion of all previous therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of cancer ≥ **X** week before the start of study therapy.
4. 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.
5. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.
6. Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

**Exclusion criteria**

An individual who meets any of the following criteria will be excluded from participation in this study:

* 1. 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 (*i.e.*, have residual toxicities > Grade 1).
	2. Patients who are receiving any other investigational agents or an investigational device within 21 days before administration of first dose of study drugs.
	3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to [IND Agent(s)] or other agents used in study.
	4. 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.
	5. Significant cardiovascular disease (eg, myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure; or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.
	6. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with [IND Agent(s)]. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated

# Vulnerable Populations

If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

* + 1. If the research involves human fetuses, review “CHECKLIST: Subpart B “to ensure that you have provided enough information.
		2. If the research involves neonates of uncertain viability or non-viable neonates, review “CHECKLIST: Subpart B” to ensure that you have provided sufficient information.
		3. If the research involves prisoners, review “CHECKLIST: Subpart C” to ensure that you have provided enough information.
		4. If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research (“children”), review the “CHECKLIST: Subpart D” to ensure that you have provided enough information.
		5. If the research involves cognitively impaired adults, review “CHECKLIST: Cognitively Impaired Adults (HRP-417)” to ensure that you have provided enough information.

# Local Number of Participants

Indicate the total number of participants to be accrued locally.

If applicable, distinguish between the number of participants who are expected to be enrolled and screened, and the number of participants needed to complete the research procedures (i.e., numbers of participants excluding screen failures.)

**Example:**

We will be recruiting X participants at Winship and X in all sites. We are expecting to have to enroll (consent) X number of participants to reach our recruitment goal of X at Winship. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

# Recruitment Methods

Describe when, where, and how potential participants will be recruited.

Describe the source of participants.

Describe the methods that will be used to identify potential participants.

Describe materials that will be used to recruit participants. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Describe the amount and timing of any payments to participants. Reimbursement for expenses/travel?

**Example**

Investigators, nurses, and/or data managers review lists of cancer patients who have cancer and will determine if there are patients who might be eligible for a clinical trial. The nurse/data manager reviews accessible medical records to screen further for eligibility. The nurse reviews the eligibility with the physician.

Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options.

Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.

Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

* Signed patient consent form
* HIPAA authorization form
* Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

**Participating Site (s)**

* A site- specific Central Subject Registration (CSR) form will be provided to each Participating Site.

After each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship’s Central Subject Registrar per instructions on the form. Once a subject is registered, each participating site will be notified via e-mail.

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.

When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, randomization and or enrollment may proceed. Oncore and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within\_\_\_\_\_\_\_\_\_\_ business days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

The Eligibility checklist is to be printed from OnCore and verified by 2 people, of which one must be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator (MSC) or designee (fax 404-778-0417) within 14 days after pre-registration but no later than 2 business days before the scheduled treatment visit. Eligibility will be confirmed by the site investigator or co-investigator and the MSC or designee within 1 business day of receipt of all eligibility documentation and confirmation will be sent to the participating site along with cohort assignment, if subject meets criteria.The Participating Site will enter all data in OnCore following eligibility confirmation, including subject ‘on treatment date’. If a consented subject does not meet eligibility criteria (screen failure), the MSC will update the enrollment status in OnCore. The Participating Site is responsible for entering data for all procedures subject completed prior to eligibility determination.

# Withdrawal of Participants

Describe anticipated circumstances under which participants will be withdrawn from the research without their consent.

Describe any procedures for orderly termination.

Describe procedures that will be followed when participants withdraw from the research, including partial withdrawal from procedures with continued data collection.

**Example:**

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

* Pregnancy
* Significant study intervention non-compliance
* If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
* Disease progression which requires discontinuation of the study intervention
* If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
* Participant unable to receive <study intervention> for [x] days/weeks.]

The reason for participant discontinuation or withdrawal from the study will be recorded on the <specify> Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, <will> or <will not> be replaced.

# Risks to Participants

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the participants related the participants’ participation in the research. Include as may be useful for the IRB’s consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

If applicable, indicate which procedures may have risks to the participants that are currently unforeseeable.

If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

If applicable, describe risks to others who are not participants.

**Example:**

* **Additional blood draws** - The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.
* **Data security-** Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects’ PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

# Potential Benefits to Participants

Describe the potential benefits that individual participants may experience from taking part in the research. Include as may be useful for the IRB’s consideration, the probability, magnitude, and duration of the potential benefits.

Indicate if there is no direct benefit. Do not include benefits to society or others.

**Example:**

There is no guarantee of benefit to subjects who enroll in this protocol.

# Data Management and Confidentiality

Describe the data analysis plan, including any **statistical procedures** or **power analysis**.

Describe the steps that will be taken **to secure the data** (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Describe any procedures that will be used for quality control of collected data.

Describe how **data or specimens will be handled** study-wide:

* What information will be included in that data or associated with the specimens?
* Where and how data or specimens will be stored?
* How long the data or specimens will be stored?
* Who will have access to the data or specimens?
* Who is responsible for receipt or transmission of the data or specimens?
* How data or specimens will be transported?

**Example:**

****16.1 Statistical consideration section: Biostatistician****

16.2 Data/specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics.

All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study CANCER TYPE. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking

# Provisions to Monitor the Data to Ensure the Safety of Participants

Describe:

* The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether participants remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor. Description of plan for notifying the IRB of reportable events; whether the sponsor requires reporting above and beyond the Emory IRB reporting requirements, and if so, a description of the requirements and plan for meeting them. See <http://irb.emory.edu/documents/DSMB-DSMPGuidance.pdf> for guidance.
* What data are reviewed, including safety data, untoward events, and efficacy data.
* How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).
* The frequency of data collection, including when safety data collection starts.
* Who will review the data.
* The frequency or periodicity of review of cumulative data.
* The statistical tests for analyzing the safety data to determine whether harm is occurring.
* Any conditions that trigger an immediate suspension of the research.

**Example:**

**Definition of Adverse Events (AE)**

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

**Definition of Serious Adverse Events (SAE)**

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

* Death
* Life-threatening adverse event
* Inpatient hospitalization or prolongation of existing hospitalization
* A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
* Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

**Classification of an Adverse Event**

Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

* **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
* **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
* **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

* **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
* **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
* **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
* **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
* **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

**Adverse Event and Serious Adverse Event Reporting**

Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment allocation/randomization through **X** days following cessation of treatment, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.

The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient’s CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)

2. Its duration (Start and end dates)

3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)

4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials).

7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase I studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator’s discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Serious Adverse Event Reporting

For the time period beginning at treatment allocation/randomization through **X** days following cessation of treatment, or **X** days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, FDA or Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

**to Pharma/IRB or FDA**.

All subjects with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.

Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

All SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following

**MedWatch 3500 Reporting Guidelines:**

Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at <http://www.fda.gov/medwatch/index.html>.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

**Reporting Requirements for IND holder**

For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar-Day Telephone or Fax Report

The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator’s Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.

FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.

The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

For participating subsites, adverse events collected at weekly treatment visits are to be entered into OnCore no later than 14 calendar days after data collection.

Site investigators must report all SAEs and unanticipated problems to the sponsor-investigator within 24 hours of the participating site becoming aware of the event. The participating site will submit the MedWatch Form 3500A to the Winship regulatory staff and will also enter the data into OnCore within the specified timelines above. The Emory sponsor must review and sign off on the event and return to the Winship regulatory staff. Regulatory will review the assessment to determine IRB and/or FDA reporting requirements.

As applicable in multi-site studies, investigative sites at each institution should report serious adverse events to their respective IRB per local IRB policies and procedures. The Principal Investigator will submit SAE reports from outside institutions to his/her institution’s IRB per institutional guidelines.

Subsite SAE Reporting Requirements

Subsites are not permitted to report directly to the coordinating center IRB or FDA. All external site SAEs are to be reported to the coordinating center. The coordinating center multi-site coordinator will facilitate submission of external site SAEs to the coordinating center IRB and FDA.

All serious adverse events (SAEs) and other adverse events must be recorded on case report forms. In addition, all SAEs must be reported to the coordinating center principal investigator and coordinating center multi-site coordinator within 24 hours of knowledge of the event using the FDA MedWatch 3500A mandatory reporting form.

Copies of de-identified source documentation pertaining to the SAE must be submitted to the coordinating center. If a patient is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up form.

All SAEs must be submitted to the local IRB per local IRB and institutional policy.

Upon request of additional data or information that is deemed necessary must be reported to the coordinating center as soon as possible but no later than 5 calendar days.

Coordinating center reporting to the food and drug administration (FDA)

The Principal Investigator, as holder of the IND (as applicable), will be responsible for all communication with the FDA. The Principal Investigator [or designee] will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but no later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information. Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800- FDA-0178) using MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at <http://www.fda.gov/medwatch/getforms.htm>.

An annual safety report containing all SAEs, expected and unexpected, will be sent to the FDA and other applicable regulatory authorities.

Expedited reporting requirements for phase 1/2 studies under IND w/in 30 days of last administration of the investigational agent/intervention

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.

**ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the Sponsoring IRB/FDA within the timeframes detailed in the table below:

|  |  |  |
| --- | --- | --- |
| **Hospitalization** | **Grade 1 and Grade 2 Timeframes** | **Grade 3-5****Timeframes** |
| Resulting in Hospitalization ≥ 24 hrs | 10 Calendar Days | 24-Hour 5 Calendar Days |
| Not resulting in Hospitalization ≥ 24 hrs | Not required |
| **Expedited AE reporting timelines are defined as:*** “24-Hour; 5 Calendar Days” - The AE must initially be reported to the IRB/FDA within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
* “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.
 |
| 1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:*** All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:*** Grade 2 AEs resulting in hospitalization or prolongation of hospitalization
 |

As applicable in multi-site trials, participating investigators should notify the Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

Second and secondary malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through **ONCORE.**

Three options are available to describe the event:

* Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
* Myelodysplastic syndrome (MDS)
* Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; 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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator’s responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI’s name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

**The Data and Safety Monitoring Committee (DSMC)**

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP). The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data. The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Multisite Monitoring Plan

 At the time of study initiation at a non-Emory site, the Emory Sponsor, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings, which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spreadsheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the Emory PI via e-mail. Multi-Site Winship’s MSC will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (once annually onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies. Select one of the following two options about the type and frequency of the teleconferences to insert into the monitoring plan: Option 1: At least monthly teleconferences between Emory PI and participating site Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The PI at Emory will communicate with participating sites via monthly email. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the principal investigators at each site. Option 2: Weekly teleconferences at working group meetings between Emory PI and participating site Teleconferences will be conducted weekly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. A record of the teleconferences will be kept in the regulatory binder.

#  Provisions to Protect the Privacy Interests of Participants

Describe the steps that will be taken to protect participants’ privacy interests. “Privacy interest” refers to a person’s desire to place limits on whom they interact or whom they provide personal information.

Describe what steps you will take to make the participants feel at ease with the research situation in terms of the questions being asked and the procedures being performed. “At ease” does not refer to physical discomfort, but the sense of intrusiveness a participant might experience in response to questions, examinations, and procedures.

Indicate how the research team is permitted to access any sources of information about the participants.

**Example:**

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived

#  Economic Burden to Participants

Describe any costs that participants may be responsible for because of participation in the research.

The study sponsor will (or will not) pay for certain items and services the subject may receive in this study. Subjects will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be

#  Consent Process

Indicate whether you will you be obtaining consent, and if so describe:

* Where will the consent process take place?
* Any waiting period available between informing the prospective subject and obtaining the consent.
* Any process to ensure ongoing consent.
* Please describe:
* The role of the individuals listed in the application as being involved in the consent process.
* The time that will be devoted to the consent discussion.
* Steps that will be taken to minimize the possibility of coercion or undue influence.
* Steps that will be taken to ensure the participants’ understanding.

Note: If you are planning to obtain consent via electronic signature, please review [this document](http://www.irb.emory.edu/documents/guidance-eICF_use.pdf). Additional guidance on consent documentation and process can be found at <http://www.irb.emory.edu/forms/consent_toolkit/guidance.html>

**Example**

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic.

At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.

Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient’s capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.

It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time.

Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent.

Prospective participants will be provided with a description of any reasonably forseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.

Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.

Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding.

All participants will be told of any additional costs that may result from participation in the research.

**Non-English-Speaking Participants**

* Indicate what language(s) other than English are understood by prospective participants or representatives.
* If participants who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those participants will be in that language. Indicate the language that will be used by those obtaining consent.
* If you checked N/A, please provide a reasoning of why subjects with limited English proficiency are exclude.
* Note: if you stated that subjects with LEP will be enrolled, you are approved for the use of the Emory IRB shortforms. Please read the guidance about the use of short forms here.

**Example:**

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1:”Obtaining Informed consent for Interventional clinical trial” will be followed.

**Participants who are not yet adults (infants, children, teenagers)**

* Describe the criteria that will be used to determine whether a prospective participant has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.)
* For research conducted in Georgia, review “Emory IRB Policies and Procedures: 53 RESEARCH INVOLVING CHILDREN – ADDITIONAL PROTECTIONS” and “46 LEGALLY AUTHORIZED REPRESENTATIVES AND SURROGATE CONSENT” to be aware of which individuals in the state meet the definition of “children.”
* For research conducted outside of Georgia, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. Please reference “Emory IRB Policies and Procedures: 53 RESEARCH INVOLVING CHILDREN – ADDITIONAL PROTECTIONS” and ” 46 LEGALLY AUTHORIZED REPRESENTATIVES AND SURROGATE CONSENT”
* Describe whether parental permission will be obtained from:
* Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
* One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.
* Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals’ authority to consent to each child’s general medical care.
* Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.
* When assent of children is obtained describe whether and how it will be documented.

**Cognitively Impaired Adults**

Describe the process to determine whether an individual is capable of consent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require children to sign assent documents.

**Adults Unable to Consent**

* List the individuals from whom permission will be obtained in order of priority. (E.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.)
* For research conducted in the state, review “46 LEGALLY AUTHORIZED REPRESENTATIVES AND SURROGATE CONSENT” to be aware of which individuals in the state meet the definition of “legally authorized representative.”
* For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research.
* Describe the process for assent of the participants. Indicate whether:
* Assent will be required of all, some, or none of the participants. If some, indicated, which participants will be required to assent and which will not.
* If assent will not be obtained from some or all participants, an explanation of why not.
* Describe whether assent of the participants will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require participants to sign assent documents.

**Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)**

* Review the [Emory IRB waiver document](http://www.irb.emory.edu/documents/Combined_Waiver_Consent_HIPAA_Elements.docx) to ensure you have provided sufficient information for the IRB to make these determinations.
* If the research involves a waiver the consent process for planned emergency research, please review the “CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)” to ensure you have provided sufficient information for the IRB to make these determinations.

#  Setting

* Describe the sites or locations where your research team will conduct the research.
* Identify where your research team will identify and recruit potential participants.
* Identify where research procedures will be performed.
* Describe the composition and involvement of any community advisory board.
* For research conducted outside of the organization and its affiliates describe:
* Site-specific regulations or customs affecting the research for research outside the organization.
* Local scientific and ethical review structure outside the organization.

**Example:**

The research will be conducted at Emory University and at additional sites:

Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, multidisciplinary tumor board at Emory University.

#  Resources Available

* Describe the resources available to conduct the research: For example, as appropriate:
* Justify the feasibility of recruiting the required number of suitable participants within the agreed recruitment period. For example, how many potential participants do you have access to? What percentage of those potential participants do you need to recruit?
* Describe the time that you will devote to conducting and completing the research.
* Describe your facilities.
* Describe the availability of medical or psychological resources that participants might need as a result of an anticipated consequences of the human research.
* Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation’s top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

**Winship Cancer Institute (Winship)** is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship’s NCI designation was renewed in 2012 and 2016, achieving an “outstanding” rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as ‘exceptional’ by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

#  Multi-Site Research when Emory is the Lead Site

*Study -Wide Number of Participants*

*If this is a multicenter study, indicate the total number of participants to be accrued across all sites.*

Study-Wide Recruitment Methods

* *If this is a multicenter study and participants will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described later in the protocol.*
* *Describe when, where, and how potential participants will be recruited.*
* *Describe the methods that will be used to identify potential participants.*
* *Describe materials that will be used to recruit participants. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)*
* *Describe the processes to ensure communication among sites. See “WORKSHEET: Communication and Responsibilities (HRP-830).” All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
* *All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site’s IRB of record).*
* *All modifications have been communicated to sites, and approved (including approval by the site’s IRB of record) before the modification is implemented.*
* *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.*
* *All local site investigators conduct the study in accordance with applicable federal regulations and local laws.*
* *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy*
* *Describe the method for communicating to engaged participating sites (see “WORKSHEET: Communication and Responsibilities (HRP-830)”):*
* *Problems (inclusive of reportable events).*
* *Interim results.*
* *The closure of a study*
* *If this is a multicenter study where you are a participating site/investigator, describe the local procedures for maintenance of confidentiality. (See “WORKSHEET: Communication and Responsibilities (HRP-830).”)*
* *Where and how data or specimens will be stored locally?*
* *How long the data or specimens will be stored locally?*
* *Who will have access to the data or specimens locally?*
* *Who is responsible for receipt or transmission of the data or specimens locally?*
* *How data and specimens will be transported locally?*

**Example:**

All sites will have the current protocol document and each IRB will review each site’s consent form and all required approvals will be obtained at each site. Any protocol modifications will be communicated to all sites with the appropriate regulatory agencies notified for their respective reviews and approvals. All engaged participating sites will safeguard date, including secure transmission of data, as required by local information security policies. All local site investigators will conduct the study in accordance with applicable federal regulations and local laws. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Site initiation at subsites

At the time of study initiation at a subsite, the coordinating center multi-site coordinator (with additional staff as needed) will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance.

Subsite data collection

Subsite data must be submitted to the coordinating center multi-site coordinator as outlined in the protocol-specific monitoring plan. The protocol-specific monitoring plan will be provided by the coordinating center multi-site coordinator to external participating prior to site activation. Access to the coordinating center OnCore database will be provided to external participating sites for direct electronic data entry. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan. All data must be entered in the timeframe required at each site, but no later than 14 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The coordinating center multi-site coordinator will provide OnCore training and request access to the appropriate staff at the participating site.

Monthly investigator conference calls

The subsite research coordinators will maintain a spreadsheet which will be de-identified and will summarize patient data for subjects actively being treated on the trial well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the coordinating center PI / IND sponsor (or designee) via e-mail. Teleconferences will be conducted at least once monthly between the PI (or designee) at Emory and the research team at the participating site(s).

The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The coordinating center (or designee) will communicate with participating sites via monthly email.

The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the research teams at subsite.

Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Subsite self-monitoring: The participating site will have internal monitoring meetings. These meetings which will include the participating site investigator (or designee), the clinical research coordinator and the regulatory affairs coordinator as applicable, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. Chart reviews will be performed on selected cases by participating site staff to confirm that the data collection is accurate regarding study conduct, data collection, documentation and completion.

Central monitoring: Study-specific monitoring plans are specified per site, with the only difference between sites whether the site submits source data on paper or provides the coordinating center multi-site team remote access to that site’s local electronic medical record. Centralized monitoring will occur minimally quarterly, no more frequently than monthly. Monitoring will be centralized, including data reporting and research sample acquisition. The coordinating center multi-site coordinator will perform on-site and/or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (on site up to once per year and at least three times remotely) until subject follow-up is terminated. Monthly reviews of data will be conducted to ensure compliance or identify discrepancies; specifically, to assess compliance with the protocol, verify informed consent forms, verify compliance with SAE reporting procedures, monitor the tracking of study drug (pharmacy visit, storage and accounting of study drug), retrieve regulatory documentation, and perform quality control by comparing data from the CRF to the source documents of the center.

Auditing

For sites with an auditing mechanism in place that are able to share documentation of their auditing standards and processes followed, an agreement may be requested for the site to perform local auditing and provide formal audit reports to the coordinating center.

#  References

*Add references*

# APPENDIX A PERFORMANCE STATUS CRITERIA

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

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

# APPENDIX B Drug Diary

|  |
| --- |
| **Study ID:** |
|
| **[***Drug***] Pill Diary** |
|  Subject Initials: **\_\_\_** Subject ID: **\_\_\_\_\_** Cycle: \_\_\_\_\_   |
|
|
| **Instructions**: |   |   |   |   |   |   |   |   |   |
| Planned Daily Dose: **\_\_mg** |  |  |  |  |  |  |   |
| REMINDERS: |
| 1.  |
| 2. |
| Day | Date  | Time | # of Tablets taken | Comments |
| 1 |  |   |   |   |
| 2 |  |   |   |   |
| 3 |  |   |   |   |
| 4 |  |   |   |   |
| 5 |  |   |   |   |
| 6 |  |   |   |   |
| 7 |  |   |   |   |
| 8 |  |   |   |   |
| 9 |  |   |   |  |
| 10 |  |   |   |   |

**Record all medications taken during this cycle for example prescriptions and over the counter including vitamins.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Name** **of**  **Medication** | **Why did you take the medication?** | **Date** **Medication** **Started** | **Date Medication Stopped** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

***If you have any questions, please call: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

# APPENDIX C Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
| --- | --- |
| ADA | Anti-drug antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALK | Anaplastic lymphoma kinase |
| ALT | Alanine aminotransferase |
| APF12 | Proportion of patients alive and progression free at 12 months from randomization |
| AST | Aspartate aminotransferase |
| BoR | Best objective response |
| BP | Blood pressure |
| C | Cycle |
| CD | Cluster of differentiation |
| CI | Confidence interval |
| CL | Clearance |
| Cmax | Maximum plasma concentration |
| Cmax,ss | Maximum plasma concentration at steady state |
| CR | Complete response |
| CSA | Clinical study agreement |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Event |
| CTLA-4 | Cytotoxic T–lymphocyte-associated antigen 4 |
| Ctrough,ss | Trough concentration at steady state |
| CXCL | Chemokine (C-X-C motif) ligand |
| DoR | Duration of response |
| EC | Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EDoR | Expected duration of response |
| EGFR | Epidermal growth factor receptor |
| EU | European Union |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| GMP | Good Manufacturing Practice |
| hCG | Human chorionic gonadotropin |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| IB | Investigator’s Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IFN | Interferon |
| IgE | Immunoglobulin E |
| IgG | Immunoglobulin G |
| IHC | Immunohistochemistry |
| IL | Interleukin |
| ILS | Interstitial lung disease |
| IM | Intramuscular |
| IMT | Immunomodulatory therapy |
| IP | Investigational product  |
| irAE | Immune-related adverse event |
| IRB | Institutional Review Board |
| irRECIST | Immune-related Response Evaluation Criteria in Solid Tumors |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| mAb | Monoclonal antibody |
| MDSC | Myeloid-derived suppressor cell |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHLW | Minister of Health, Labor, and Welfare |
| miRNA | Micro-ribonucleic acid |
| MRI | Magnetic resonance imaging |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| NSCLC | Non–small-cell lung cancer |
| OAE | Other significant adverse event |
| ORR | Objective response rate |
| OS | Overall survival |
| PBMC | Peripheral blood mononuclear cell |
| PD | Progressive disease |
| PDx | Pharmacodynamic(s) |
| PFS | Progression-free survival |
| PFS2 | Time to second progression |
| PGx | Pharmacogenetic research |
| PK | Pharmacokinetic(s) |
| PR | Partial response |
| q2w | Every 2 weeks |
| q3w | Every 3 weeks |
| q4w | Every 4 weeks |
| q6w | Every 6 weeks |
| q8w | Every 8 weeks |
| QTcF | QT interval corrected for heart rate using Fridericia’s formula |
| RECIST 1.1 | Response Evaluation Criteria in Solid Tumors, version 1.1 |
| RNA | Ribonucleic acid |
| RR | Response rate |
| RT-QPCR | Reverse transcription quantitative polymerase chain reaction |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Safety analysis set |
| SCLC | Small cell lung cancer |
| SD | Stable disease |
| SNP | Single nucleotide polymorphism |
| SoC | Standard of Care |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TSH | Thyroid-stimulating hormone |
| ULN | Upper limit of normal |
| US | United States |
| WBDC | Web-Based Data Capture |
| WHO | World Health Organization |