**UCCC CTO PROTOCOL TEMPLATE INSTRUCTIONS**

**Version Date 15 SEPT 2020**

**Please ensure you also complete the form HRP-508 which is a UC IRB required supplement when using the NCI/CTO protocol template.**

This is a template that is most applicable for oncology studies involving investigational drug. If your study will consist of only sample collection, data review, or you will be working with a device, please contact the UCCC Clinical Trials Office for a different protocol template for use with these types of studies. This protocol has been modified from the NCI template.

Please contact the UCCC CTO for any questions

Missy Racic, IITC & - [BRAUCKMA@ucmail.uc.edu](mailto:BRAUCKMA@ucmail.uc.edu)

Nicky Kurtzweil, UCCC CTO QA & Data Manager – [kurtzwny@ucmail.uc.edu](mailto:kurtzwny@ucmail.uc.edu)

Christine Vollmer, Regulatory Manager (IND/IDE questions) mccordce@ucmail.uc.edu

Depending on the phase of the study and whether it is a single-agent or combination agent study, include sections as follows:

* No highlighting = for all protocols
* Yellow highlighting = for phase 1 protocols
* Green highlighting – for phase 2 protocols
* Blue highlighting – for combination agent protocols
* Pink highlighting – for advanced imaging protocols

**SUMMARY OF PROTOCOL CHANGES**

For Protocol Amendment # to: **N/A - Original**

UCCC Protocol #: [**This will be provided to you by the UCCC PRMC Coordinator, if you are unsure please leave blank or as TBD**]

Protocol Date: **N/A**

*Please provide a list of changes from the previous approved version of the protocol. The list must identify by page and section each change made to a protocol document. All changes must be described in a point-by-point format (*i.e.*, Page 3, section 1.2, replace ‘xyz’ and insert ‘abc’). When appropriate, a brief justification for the change should be included.*

| **#** | **Section** | **Change** |
| --- | --- | --- |
| 1. |  |  |
| 2. |  |  |
| 3. |  |  |
| 4. |  |  |
| 5. |  |  |

**UCCC Protocol #:** TBD

**ClinicalTrials.gov Identifier:** TBD

**Study Title:** Please insert your protocol title

|  |  |
| --- | --- |
| **Principal Investigator:** | Name  Institution  Address  Telephone  e-mail address |
| **Sub-Investigators:** | Name  Title  Institution  Name  Title  Institution  Name  Title  Institution |
| **Statistician:** | Name  Title  Institution |
| **Participating Sites** | University of Cincinnati Cancer Center  *List Names of any other participating centers* |

**IND #:** *Remove or TBD*

**IND Sponsor:** *Remove or TBD*

*OR*

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

**IDE #:** *Remove or TBD*

**IDE Sponsor**: *Remove or TBD*

**Device Name:**

**Protocol Type / Version # / Version Date: Original / Version 1/** DATE

# SCHEMA

*Please provide a schema for the study. If preferred, a summary or synopsis may be provided.*

*If appropriate, a table may be used to describe the regimen; see examples below for phase 1 single-agent and combination dose-escalation protocols. The table should include the route of administration (PO, IV,* etc.*) and dosing schedule (QD, BID, Days 1-5,* etc.*).*

*For phase 1 single-agent protocols:*

|  |  |
| --- | --- |
| **Dose Escalation Schedule** | |
| **Dose Level** | Dose of *[CTEP IND Agent]\** |
| Level 1 |  |
| Level 2 |  |
| Level 3 |  |
| Level 4 |  |
| Level 5 |  |
| *\* Doses are stated as exact dose in units (*e.g.*, mg/m2, mcg/kg,* etc.*) rather than as a percentage.* | |

*For phase 1 combination protocols:*

|  |  |  |  |
| --- | --- | --- | --- |
| **Dose Escalation Schedule** | | | |
| **Dose Level** | **Dose\*** | | |
| ***Agent X***  ***(units)*** | ***Agent Y***  ***(units)*** | ***Agent Z***  ***(units)*** |
| Level 1 |  |  |  |
| Level 2 |  |  |  |
| Level 3 |  |  |  |
| Level 4 |  |  |  |
| Level 5 |  |  |  |
| *\*Doses are stated as exact dose in units (*e.g.*, mg/m2, mcg/kg,* etc.*) rather than as a percentage.* | | | |

*For phase 2 single-agent or combination protocols, provide study-specific schema or synopsis.*

*Please indicate when advanced imaging will be performed in the study.*

**TABLE OF CONTENTS**

[SCHEMA 2](#_Toc39157015)

[1. OBJECTIVES 6](#_Toc39157016)

[1.1 Primary Objectives 6](#_Toc39157017)

[1.2 Secondary Objectives 6](#_Toc39157018)

[1.3 Exploratory Objectives 6](#_Toc39157019)

[1.4 Primary Endpoints 6](#_Toc39157020)

[1.5 Secondary Endpoints 6](#_Toc39157021)

[1.6 Exploratory Endpoints 6](#_Toc39157022)

[2. BACKGROUND 7](#_Toc39157023)

[2.1 *Insert Name of the Study Disease(s)* Background 7](#_Toc39157024)

[2.2 *Insert Name of the Drug/Device/Agent to be studied* Background 7](#_Toc39157025)

[2.3 *Insert Name of the Other Drug/Device/Agent(s)* Background 7](#_Toc39157026)

[2.4 Rationale 7](#_Toc39157027)

[2.5 Correlative Studies Background 7](#_Toc39157028)

[3. PATIENT SELECTION 8](#_Toc39157029)

[3.1 Eligibility Criteria 8](#_Toc39157030)

[3.2 Exclusion Criteria 10](#_Toc39157031)

[3.3 Inclusion of Women and Minorities 11](#_Toc39157032)

[4. REGISTRATION PROCEDURES 11](#_Toc39157033)

[4.1 Patient Registration 11](#_Toc39157034)

[4.2 General Guidelines 11](#_Toc39157035)

[5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES 11](#_Toc39157036)

[5.1 Biomarker Plan 11](#_Toc39157037)

[5.2 Integral Laboratory or Imaging Studies 16](#_Toc39157038)

[5.3 Investigational Device Information 16](#_Toc39157039)

[5.4 Integrated Correlative Studies 16](#_Toc39157040)

[5.5 Exploratory/Ancillary Correlative Studies 16](#_Toc39157041)

[5.6 Special Studies 17](#_Toc39157042)

[6. TREATMENT AND/OR IMAGING PLAN 17](#_Toc39157043)

[6.1 Assignment of Screening and Subject Numbers 17](#_Toc39157044)

[6.2 Medical History 17](#_Toc39157045)

[6.3 Prior and Concomitant Medications 18](#_Toc39157046)

[6.4 Adverse Events 18](#_Toc39157047)

[6.5 Agent Administration 18](#_Toc39157048)

[6.6 *For phase 1 protocols only:* Definition of Dose-Limiting Toxicity 21](#_Toc39157049)

[6.7 Dose Expansion Cohorts: 22](#_Toc39157050)

[6.8 Clinical Procedures and Assessments 22](#_Toc39157051)

[6.9 Visit Requirements 24](#_Toc39157052)

[6.10 Withdrawal/Discontinuation 25](#_Toc39157053)

[6.11 General Concomitant Medication and Supportive Care Guidelines 25](#_Toc39157054)

[6.12 Contraception/Birth Control 25](#_Toc39157055)

[6.13 Breast Feeding 26](#_Toc39157056)

[6.14 Duration of Therapy 26](#_Toc39157057)

[6.15 Duration of Follow-Up 26](#_Toc39157058)

[7. DOSING DELAYS/DOSE MODIFICATIONS 27](#_Toc39157059)

[8. PHARMACEUTICAL and/or IMAGING AGENT INFORMATION 29](#_Toc39157060)

[8.1 Insert Research Drug or Agent Name Pharmaceutical Information) 30](#_Toc39157061)

[8.2 Other Investigational Agent(s) 30](#_Toc39157062)

[8.3 Commercial Agent(s) 31](#_Toc39157063)

[9. STATISTICAL CONSIDERATIONS 32](#_Toc39157064)

[9.1 Study Design/Endpoints 32](#_Toc39157065)

[9.2 Sample Size/Accrual Rate 33](#_Toc39157066)

[9.3 Stratification Factors 33](#_Toc39157067)

[9.4 Analysis of Secondary Endpoints 33](#_Toc39157068)

[9.5 For phase 2 protocols only: Reporting and Exclusions 33](#_Toc39157069)

[10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS 34](#_Toc39157070)

[10.1 Listing of Known Risks of *Insert Drug Name or Research Intervention* 34](#_Toc39157071)

[10.2 Adverse events 34](#_Toc39157072)

[10.3 Serious Adverse events 35](#_Toc39157073)

[10.4 Reporting of Serious Adverse Events 35](#_Toc39157074)

[10.5 Averse event collection and reporting 36](#_Toc39157075)

[10.6 Collection and Recording of Adverse Events 36](#_Toc39157076)

[10.7 Follow-Up of Adverse Events 36](#_Toc39157077)

[10.8 Adverse Event Grading 36](#_Toc39157078)

[10.9 Pregnancy 37](#_Toc39157079)

[10.10 Secondary Malignancy 37](#_Toc39157080)

[10.11 Second Malignancy 37](#_Toc39157081)

[11. STUDY CALENDAR 37](#_Toc39157082)

[12. MEASUREMENT OF EFFECT 39](#_Toc39157083)

[12.1 Antitumor Effect – Solid Tumors 39](#_Toc39157084)

[12.2 Antitumor Effect – Hematologic Tumors 46](#_Toc39157085)

[12.3 Other Response Parameters 46](#_Toc39157086)

[13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS 46](#_Toc39157087)

[13.1 Study Oversight 46](#_Toc39157088)

[13.2 Data Reporting 46](#_Toc39157089)

[13.3 SMART IRB 47](#_Toc39157090)

[13.4 Genomic Data Sharing Plan 48](#_Toc39157091)

[14. REFERENCES 49](#_Toc39157092)

[APPENDIX A PERFORMANCE STATUS CRITERIA 50](#_Toc39157093)

[APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE 51](#_Toc39157094)

# OBJECTIVES

## Primary Objectives

* + 1. *Please add in your primary objective(s)*
    2. *Please add in your primary objective(s)*

*Please specify advanced imaging Primary Objective if applicable.*

## Secondary Objectives

* + 1. *Please add in your secondary objective(s)*
    2. *Please add in your secondary objective(s)*
    3. *[All phase 1 studies must include the following text as a secondary objective.]* To observe and record anti-tumor activity. Although the clinical benefit of [this/these] drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

*Please specify advanced imaging Secondary/Exploratory Objective if applicable.*

## Exploratory Objectives

* + 1. Please add in your exploratory objective(s)

# BACKGROUND

## *Insert Name of the Study Disease(s)* Background

*Please provide background information on the study disease. Ensure you insert your references at the end of this protocol (there is no limit on the number of references). It is helpful to note the normal standard of care or clinical practice for treatment here as well as incidence rates to help support your rationale later for use of the new research device/interventions.*

## *Insert Name of the Drug/Device/Agent to be studied* Background

*Please provide background information below on the drug/device/agent you are researching. Include information to support safety issues and the rationale for the proposed starting dose, dose escalation scheme, and regimen chosen. Please also provide information on the mechanism of action, summaries of nonclinical and clinical studies, nonclinical and clinical pharmacokinetics, and major route of elimination. If available, please include information on the metabolism of the study agent in humans and its potential for drug interactions, if any interactions (*e.g.*, via the P450 enzyme system).*

*Please include information regarding the rationale for advanced imaging as appropriate; include information on the pharmacology, toxicology, and previous human imaging studies from the current Investigator’s Brochure as applicable*. ***For complete information, please refer to the current Investigator’s Brochure:*** *[Insert title, version and date of NCI/CIP IB]. Contact CIP regulatory staff at* [*NCICIPINDAGENTS@mail.nih.gov*](mailto:NCICIPINDAGENTS@mail.nih.gov) *for the current Investigator’s Brochure.*

## *Insert Name of the Other Drug/Device/Agent(s)* Background

*Please provide background information on other agent(s) and/or treatments in this study, including information to support safety issues and the rationale for the proposed starting dose and dose escalation scheme, if applicable.*

## Rationale

*Please provide the background and rationale for this therapy/combination therapy/advanced imaging (in this disease). State the problem or question (e.g., describe the population, disease, current standard of care, if one exists, and limitations of knowledge or available therapy referring your sections above) and the reason for conducting the clinical trial.*

*Describe the rationale for the type of study design (e.g., non-inferiority as opposed to superiority). Discuss known or potential problems associated with the study design (e.g., control groups).*

## Correlative Studies Background

*Please provide background information on each planned correlative study including the biologic rationale and hypothesis as well as the relevant preclinical and clinical (if available) data. Refer to “Guidelines for Correlative Studies in Clinical Trials” (*[*http://ctep.cancer.gov/protocolDevelopment/templates\_applications.htm*](http://ctep.cancer.gov/protocolDevelopment/templates_applications.htm)*).*

*If this trial includes no correlative studies, this section can be deleted.*

# PATIENT SELECTION: Eligibility

## Inclusion Criteria

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

*OR*

Patients must have histologically or cytologically confirmed *[Study Disease]*

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

*Note: Radiological evaluation should occur within approximately 30 days prior to enrollment initiation. Studies using progression-free survival (PFS) as an endpoint will require a stricter window for radiological evaluation.*

* + 1. *For phase 2 protocols:* *Please insert appropriate criteria for the particular patient population. Note: Lesions are either measurable or non-measurable using the criteria provided in Section 12 (Measurement of Effect). The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy. Suggested text is provided below.*

Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 12 (Measurement of Effect) for the evaluation of measurable disease.

*OR*

*Please insert appropriate criteria for diseases other than solid tumors. Criteria for selected hematologic malignancies can be found in the following references: J Clin Oncol 17(4):1244-53, 1999 (non-Hodgkin's lymphoma); J Clin Oncol 8(5):813-19, 1990 (acute myeloid leukemia); and Blood 887(12):4990-97, 1996 (chronic lymphocytic leukemia).*

* + 1. *Please state allowable type and amount of prior therapy. Define as appropriate any limitations on prior therapy and the time from last prior regimen (*e.g.*, no more than 6 cycles of an alkylating agent; no more than 450 mg/m2 doxorubicin for agents with expected cumulative cardiotoxicity). Include separate definitions for duration as needed (*e.g.*, at least 4 weeks since prior chemotherapy or radiation therapy, 6 weeks if the last regimen included BCNU or mitomycin C). Include site/total dose for prior radiation exposure as needed (*e.g.*, no more than 3000 cGy to fields including substantial marrow).*
    2. Age ≥18 years.
    3. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
    4. Patients must have adequate organ and marrow function as defined below:
* leukocytes ≥3,000/mcL
* absolute neutrophil count ≥1,500/mcL
* platelets ≥100,000/mcL
* total bilirubin ≤ institutional upper limit of normal (ULN)
* AST(SGOT)/ALT(SGPT) ≤3 × institutional ULN
* creatinine ≤ institutional ULN

OR

* glomerular filtration rate (GFR) *[For Phase 1]*≥60 mL/min/1.73 m2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73 m2 (see Appendix B)

*[OR for larger phase 2 or 3]*

≥50 mL/min/1.73 m2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73 m2 (see Appendix B).

* + 1. Known human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
    2. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
    3. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with known HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
    4. Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression. (*Note: In specific trials, it may be necessary to add a time factor regarding the follow-up brain imaging, but this should be as lenient as medically indicated.)*
    5. Patients with **new or progressive brain metastases** (active brain metastases) or **leptomeningeal disease** are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.
    6. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
    7. 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.
    8. *Please insert other appropriate eligibility criteria.*
    9. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry 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 4 months after completion of *[DRUG NAME]* administration.
    10. Ability to understand and the willingness to sign a written informed consent document.

## Exclusion Criteria

* + 1. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.
    2. Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia.
    3. Patients who are receiving any other investigational agents. Patients who have received other investigational agents previously who are no longer receiving these investigational agents may be eligible at the discretion of the PI.
    4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to *[Drug Name(s) under study]*
    5. *Please state appropriate exclusion criteria relating to concomitant medications or substances that have the potential to affect the activity or pharmacokinetics of the study agent(s). Examples of such agents or substances include those that interact through the CYP450 isoenzyme system or other sources of drug interactions (*e.g.*, P-glycoprotein). Specifically excluded substances may be listed below, stated in Section 8 (Pharmaceutical Information), and presented as an appendix. If appropriate, the following text concerning CYP450 interactions may be used or modified.*

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

* + 1. Patients with uncontrolled intercurrent illness that would prevent receipt of [select all that apply *investigational product or standard of care chemotherapy, radiation or surgery*].
    2. Patients with psychiatric illness/social situations that would limit compliance with study requirements.
    3. Pregnant women are excluded from this study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother withbreastfeeding should be discontinued if the mother is treated with *[Drug(s)]*
    4. *Please insert other appropriate agent-specific exclusion criteria.*

## Inclusion of Women and Minorities

Women and minorities will be included.

# REGISTRATION PROCEDURES

## Assignment of Screening and Subject Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to eligibility being confirmed. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

**Add in as applicable per PI’s preference**

* [“If a subject is not found to be eligible (screen-fails) due to not meeting the following eligibility criteria, then a subject will not be able to be re-screened” OR add in “subjects who screen-fail for any reason will be able to be re-screened” OR “subjects who screen-fail should never be re-screened for enrollment to this study.”]

Any subject who is re-screened will be provided with a new screening number for each instance for which they are being screened. The screening number will be their study number as well once they are confirmed to be eligible and registered to treatment.

## Patient Screening

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

* Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.
* For women of reproductive potential, a serum pregnancy test will be performed within 7 days prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria as long as they have not yet started treatment; however, the cost of re-screening tests will not be covered by the study. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

## Patient Registration

To determine if a patient meets eligibility criteria, the following documents should be compiled by research team and provided to the University of Cincinnati PI *and UC Project Manager* as soon after the subject has consented as possible:

* Study informed consent form signed and dated by the patient.
* Source documents verifying every inclusion and exclusion criteria for the patient.

Upon receipt, the UC PI or qualified designee will confirm subject eligibility. Eligibility must be confirmed prior to the initiation of any study procedures. Once eligibility is confirmed, a research team member may then proceed to register the subject to enrolled status within the study EDC.

## General Guidelines

Following registration, patients should begin protocol treatment within 28 days.Issues that would cause significant treatment delays should be discussed with the Principal Investigator.

# BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

## Biomarker Plan

*Use the table below to provide the study biomarker plan. List the* ***priority*** *(1, 2, 3,* etc.*);* ***biomarker name*** *(*e.g.*, specific gene mutations, proteins, cells,* etc.*);* ***biomarker assay*** *(*e.g.*, whole exome sequencing [WES], RNA sequencing [RNA-Seq], immunohistochemistry [IHC], flow cytometry,* etc.*);* ***biomarker type*** *(*i.e.*, integral, integrated, or exploratory) and* ***purpose*** *(*e.g.*, for eligibility criterion, to correlate findings with response to agent[s],* etc.*); whether biomarker is* ***“M” (mandatory) or “O” (optional)****;* ***timing*** *of the assay (*e.g.*, baseline, post-progression, upon meeting a pre-specified efficacy endpoint,* etc.*);* ***specimen*** *type (*e.g.*, fresh tumor tissue [FFPE], frozen tumor tissue, blood, serum, plasma,* etc.*);* ***quantity needed*** *(*e.g.*, number of needed cores or slides for tumor tissue or tubes for blood, volume of blood,* etc.*); and name of* ***laboratory*** *conducting the assay.*

*Note that integral biomarkers must be listed as mandatory, whereas integrated and exploratory biomarkers can be either mandatory or optional.*

*Please also briefly describe, in text form, the overall rationale for the biomarker plan and all tissue collection and biomarker/correlative assays. If multiple assays will require use of a limited amount of tumor tissue, indicate how the use of tissue will be prioritized.*

**List of Biomarker Assays in Order of Priority**

| **Priority** | **Biomarker Name** | **Biomarker Assay** | **Biomarker Type and Purpose** | **M/O** | **Timing** | **Specimen** | **Quantity Needed** | **Laboratory** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | *[Add biomarker name]* | *[Add biomarker assay]* | *Integral*  *[Add relevant text]* | M | *[Add relevant timepoints]* | *[Add specimen type]* |  | *[Add laboratory name]* |
| 2 | *[Add biomarker name]* | *[Add biomarker assay]* | *Integrated*  [*Add relevant text]* | *[Add M or O]* | *[Add relevant timepoints]* | *[Add specimen type]* |  | *[Add laboratory name]* |
| 3 | *[Add biomarker name]* | *[Add biomarker assay]* | *Exploratory*  *[Add relevant text]* | *[Add M or O]* | *[Add relevant timepoints]* | *[Add specimen type]* |  | *[Add laboratory name]* |

*Renumber/reprioritize and add/delete rows as needed for planned correlative studies.*

**Specimen Collection Schedule**

*Please provide the type of specimen and the timepoint (study cycle/day) of each specimen collection procedure, and mark the appropriate boxes with an “X” to denote collection on that study day.*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Specimen Type** | **Baseline (Pre-treatment)** | ***[Timepoint #2]*** | ***[Timepoint #3]*** | ***[Timepoint #4]*** | ***[Timepoint #5]*** | ***[Timepoint #6]*** | ***[Timepoint #7]*** |
| *Specimen type #1* | *X* |  |  |  |  |  |  |
| *Specimen type #2* | *X* |  |  |  |  |  |  |

*Please briefly describe each planned correlative study in the appropriate subsection(s) below.*

*The description for* ***each proposed biomarker study*** *should include specific information, as outlined below (where applicable).*

1. *Provide a hypothesis and rationale for biomarker utility and a description of the impact on therapeutic agent development based on the following considerations:*
   1. *Biological and/or mechanistic rationale with data to support relationship between biomarker and agent effects*
   2. *Intended use within the proposed study*
   3. *Preclinical* in vitro *and* in vivo*, and clinical results, if applicable*
2. *Describe the assay method’s appropriateness for the study*
3. *Describe the investigator’s and clinical laboratory’s experience and competence with the proposed assays*
4. *Provide the data supporting the degree of biomarker “fit for purpose” and clinical qualification - these data should include reliability of analytical performance*
5. *It is recommended that the templates for IHC, ISH or Somatic Mutations be used for describing the status of assays, especially those that are intended to be for integral or integrated markers; these can be found on the CDP website (*[*http://www.cancerdiagnosis.nci.nih.gov/scientific\_programs/pacct/templates.htm*](http://www.cancerdiagnosis.nci.nih.gov/scientific_programs/pacct/templates.htm)*)*
6. *Justify the number of patients and specimens:*
   1. *To demonstrate feasibility*
   2. *To demonstrate that studies are likely to produce interpretable and meaningful results*
7. *Give thoughtful consideration to the risk to the patient of obtaining samples, specimens, or data for biomarker studies in the context of data on biomarker validity and degree of clinical qualification*

***Explicit instructions for handling, preserving, and shipping specimens should be provided****. If samples will be shipped to a central laboratory for processing and analysis, responsible parties and contact information should be provided in addition to instructions for handling, preserving, and shipping the specimens.*

*A plan for statistical analysis of the results of the correlative study(ies) should be provided in Section 9.4, Analysis of Secondary Endpoints.*

*For all biomarker studies, please specify whether the study is “integral,” “integrated,” or “ancillary/exploratory,” as defined by Dancey* et al. *(“Guidelines for the Development and Incorporation of Biomarker Studies in Early Clinical Trials of Novel Agents*.” Clin Cancer Res. *2010; 16:1745-55.). For example, an “integral” bioassay is one that is necessary for the trial to proceed,* i.e., *the outcome determines patient disposition. Note especially that if integral markers are to be used to make individual patient decisions, then CLIA regulations will apply (*[*http://wwwn.cdc.gov/CLIA/Default.aspx*](http://wwwn.cdc.gov/CLIA/Default.aspx)*).*

*If development of diagnostic assays to identify patients who might benefit from a molecularly targeted therapy is planned, validation in a central reference laboratory, tissue banking, and standardization of procedures is of high importance. Information on endpoint validation including additional background (as needed), description of the assay(s) used, materials and methods, and assay validation should be provided in an appendix (see also the instructions under Section 5.2, Integral Laboratory or Imaging Studies).*

*A format for presentation of the required information is shown below.*

## Integral Laboratory or Imaging Studies

* + 1. *Title – Integral Laboratory Correlative Study #1*
       1. Collection of Specimen(s)
       2. Handling of Specimens(s)
       3. Shipping of Specimen(s)
       4. Site(s) Performing Correlative Study
    2. *Title – Integral Laboratory Correlative Study #2*
       1. Collection of Specimen(s)
       2. Handling of Specimens(s)
       3. Shipping of Specimen(s)
       4. Site(s) Performing Correlative Study

## Investigational Device Information

*If an investigational device requiring an IDE is to be used in this trial, please provide the IDE #, IDE title, and the IDE sponsor. This section should be deleted if no investigational devices requiring an IDE are used.*

## Integrated Correlative Studies

* + 1. *Title – Integrated Laboratory Correlative Study #1*
       1. Collection of Specimen(s)
       2. Handling of Specimens(s)
       3. Shipping of Specimen(s)
       4. Site(s) Performing Correlative Study
    2. *Title – Integrated Laboratory Correlative Study #2*
       1. *Collection of Specimen(s)*
       2. *Handling of Specimens(s)*
       3. *Shipping of Specimen(s)*
       4. *Site(s) Performing Correlative Study*

## Exploratory/Ancillary Correlative Studies

* + 1. *Title – Exploratory/Ancillary Laboratory Correlative Study #1*
       1. Collection of Specimen(s)
       2. Handling of Specimens(s)
       3. Shipping of Specimen(s)
       4. Site(s) Performing Correlative Study
    2. *Title – Exploratory/Ancillary Laboratory Correlative Study #2*
       1. Collection of Specimen(s)
       2. Handling of Specimens(s)
       3. Shipping of Specimen(s)
       4. Site(s) Performing Correlative Study

## Special Studies

* + 1. *Title – Special Correlative Study #1*
       1. *Outcome Measure*
       2. *Assessment*
          1. *Method of Assessment*
          2. *Timing of Assessment*
       3. *Data Recording*
          1. *Method of Recording*
          2. *Timing of Recording*

# TREATMENT AND/OR IMAGING PLAN

**The Study Calendar - Section TBD** summarizes the trial procedures to be performed at each visit.

## 

## Agent Administration

Treatment will be administered on an *[inpatient/outpatient]* basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

*For phase 1 dose-escalation protocols: State the starting dose of each agent and describe the dose escalation scheme and treatment regimen.*  ***Use exact doses rather than percentages****. If appropriate, a table may be used to describe the regimen; see examples below for phase 1 single-agent and combination protocols. Please refer to the CTEP website (*[*http://ctep.cancer.gov/protocolDevelopment/policies\_nomenclature.htm*](http://ctep.cancer.gov/protocolDevelopment/policies_nomenclature.htm)*) for Guidelines for Treatment Regimen Nomenclature and Expression.*

*The table may include the route of administration (PO, IV,* etc.*) and dosing schedule (QD, BID, Days 1-5,* etc.*). Alternatively, this information may be presented in a separate “Regimen Description” table (see below for an example).*

*Example for phase 1 single-agent protocols:*

|  |  |
| --- | --- |
| **Dose Escalation Schedule** | |
| **Dose Level** | Dose of *[CTEP IND Agent]\** |
| Level 1 |  |
| Level 2 |  |
| Level 3 |  |
| Level 4 |  |
| Level 5 |  |
| *\* Doses are stated as exact dose in units (*e.g.*, mg/m2, mcg/kg,* etc.*) rather than as a percentage.* | |

*Examples for phase 1 combination protocols:*

|  |  |  |  |
| --- | --- | --- | --- |
| **Dose Escalation Schedule** | | | |
| **Dose Level** | **Dose\*** | | |
| ***[Agent X]***  ***(units)*** | ***[Agent Y]***  ***(units)*** | ***[Agent Z]***  ***(units)*** |
| Level 1 |  |  |  |
| Level 2 |  |  |  |
| Level 3 |  |  |  |
| Level 4 |  |  |  |
| Level 5 |  |  |  |
| *\*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* |
| *\*\*Doses as appropriate for assigned dose level.* | | | | | |

*For phase 2 protocols: Please describe the regimen (agent, dose, route, and schedule; the sample “Regimen Description” table above may be used, or another table format) and state any special precautions or warnings relevant for investigational study agent administration (*e.g.*, incompatibility of the agent with commonly used intravenous solutions, necessity of administering agent with food, how to round a dose of oral agent to available tablet/capsule strengths, premedications,* etc.*). Please refer to the CTEP website (*[*http://ctep.cancer.gov/protocolDevelopment/policies\_nomenclature.htm*](http://ctep.cancer.gov/protocolDevelopment/policies_nomenclature.htm)*) for Guidelines for Treatment Regimen Expression and Nomenclature.*

*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 will be returned to clinic staff at the end of each course.”*

* + 1. Study Drugs/Agents(s)

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

* + 1. Other Agent(s)

*Please describe in detail any prophylactic or supportive care regimens required for administration of each other agent in the treatment and**state any special precautions or relevant warnings (*e.g.*, incompatibility of agent with commonly used intravenous solutions, necessity of administering agent with food, premedications,* etc.*).*

* + 1. Other Modality(ies) or Procedures

*Please provide a detailed description of any other modalities (*e.g.*, surgery, radiotherapy) or procedures (*e.g.*, hematopoietic stem cell transplantation) used in the protocol treatment. If this study involves no other modalities or procedures, this section should be marked “N/A”.*

* + 1. Investigational Imaging Agent Administration

*Please describe the imaging agent regimen (agent, dose, route, schedule, timing relative to imaging, special precautions or procedures, required pre-administration lab parameters [*e.g.*, blood glucose]) for imaging agent administration.*

*Please provide the following sections:*

Image Acquisition Details:

Image Analysis Details:

Image Interpretation Details (including whether there will be local and/or central review, etc.):

Imaging Related Procedures:

## *For phase 1 protocols only:* 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.*

Management and dose modifications associated with the above adverse events are outlined in Section 7.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above. *An alternative dose-escalation design of the investigator's choice may be substituted, but should be fully detailed here, and a supporting rationale should be provided in this protocol (e.g. in the introduction/background). An example (accelerated titration) can be found on the following website (*[*http://linus.nci.nih.gov/~brb/Methodologic.htm*](http://linus.nci.nih.gov/~brb/Methodologic.htm)*)*.

|  |  |
| --- | --- |
| **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.   * If 0 of these 3 patients experience DLT, proceed to the next dose level. * 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. |

## Dose Expansion Cohorts:

Once the RP2D is reached, an additional *[insert #; suggest 6]* will be treated at this dose. For the expansion cohort, patients will continue to be monitored for occurrence of DLT. If 2 of the first 5 patients or if ≥2 of 6 patients experience DLT, the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D. *[Trials using Medidata Rave must keep the following sentence; other protocols may adapt the language in accordance with the monitoring method being used:]* Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

## General Concomitant Medication and Supportive Care Guidelines

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phases of this trial:

* Biological therapy
* Immunotherapy not specified in this protocol
* Investigational agents other than STUDY DRUG
* Live vaccines within **14** days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

Subjects, who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management other than specified as allowed, should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

## Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for *[# cycles]* or until one of the following criteria applies:

* Disease progression
* Intercurrent illness that prevents further administration of treatment
* Unacceptable adverse event(s)
* Patient decides to withdraw from the study treatment
* General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
* Clinical progression
* Patient non-compliance
* Pregnancy
  + All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
* Termination of the study by University of Cincinnati PI
* The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the study EDC (REDCAP) and within study source documentation.

## Duration of Follow-Up

Patients will be followed for *[survival up to # years after removal from study or a # of* *weeks/days; minimum of 30 days, or longer depending on the specific agent and protocol]* after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

* + 1. Post-Treatment Visits/Safety Follow-Up

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

* + 1. Survival Follow-up

Once a subject experience confirmed progression or starts a new anti-cancer therapy, the subject

moves into the survival follow-up phase and should be contacted by telephone or seen in clinic

every # weeks +/- 2 weeks to assess for survival status until death, withdrawal of consent, or at

the end of the study, whichever occurs first. Patients will be followed up to 5 years.

## Withdrawal/Discontinuation

When a subject discontinues/withdraws to active treatment prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in **Section TBD**. Patients have the option of withdrawing from treatment only (therefore entering survival follow-up) or withdrawing from study. This should be documented clearly in the study EDC (REDCap) and within source documentation.

# Other Research Activity specifications

## 

**The Study Calendar - Section TBD** summarizes the trial procedures to be performed at each visit.

## Medical History

A medical history for each subject will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

Medical history must be graded per CTCAE v.5 to facilitate the identification of grade changes from baseline. Subjects will be asked about their medical conditions at each study visit (e.g., any new admissions or changes in existing conditions) and new medical history, if any, will be recorded throughout the study.

## Prior and Concomitant Medications

Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirements, and record prior medication taken by the subject within 28 days before starting the trial (time of consent). Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the subject during the trial.

## Adverse Events

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Calendar or more frequently if clinically indicated.

Please refer to **section TBD** for detailed information regarding the assessment and recording and reporting of AEs.

## Full Physical Exam

The Investigator or qualified designee will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Full physical exam requires assessment of major organ sites (Constitutional, Head and Neck, Cardiovascular, Pulmonary, Abdominal, Musculoskeletal, Lymph, Neurological, and Skin).

## Directed Physical Exam

Except for at screening, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

## Vital Signs

The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Study Calendar. Vital signs should include: temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

## Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess ECOG status **(see Appendix A)** at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Study Calendar.

## Tumor Imaging and Assessment of Disease

Only the Investigator or qualified designee (MD only) may determine the assessment of disease recurrence.*Add in more detail relating to how this will be conducted base on your study needs.*

Patients will undergo imaging (SPECIFY – for example CT of affected target areas- ideally CT with contrast unless contraindication; MRI also acceptable) every # weeks. If patient has a PR or CR, confirmation scans are required at # weeks after scan in which response was first observed.

## Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

**Table 5. Laboratory Tests**

| **Hematology** | **Chemistry** | **Urinalysis** | **Other** |
| --- | --- | --- | --- |
| Hematocrit | Albumin | Blood | Serum β-human chorionic gonadotropin† |
| Hemoglobin | Alkaline phosphatase | Glucose | (β-hCG) † |
| Platelet count | Alanine aminotransferase (ALT) | Protein | Total triiodothyronine (T3) |
| WBC (total and differential) | Aspartate aminotransferase (AST) | Specific gravity | Free thyroxine (T4) |
| Red Blood Cell Count | CO2 or bicarbonate | Microscopic exam *(If abnormal)* | Thyroid stimulating hormone (TSH) |
| Absolute Neutrophil Count | Uric Acid | Urine pregnancy test † | Prothrombin time PT/INR |
| Absolute Lymphocyte Count | Calcium |  | Partial Thromboplastin Time (PTT) |
|  | Chloride |  |  |
|  | Glucose |  |  |
|  | Phosphorus |  |  |
|  | Potassium |  |  |
|  | Sodium |  |  |
|  | Creatinine |  |  |
|  | Magnesium |  |  |
|  | Total Bilirubin |  |  |
|  | Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)* |  |  |
|  | Total protein |  |  |
|  | Blood Urea Nitrogen |  |  |
| † Done on all women of child-bearing potential | | | |

# DOSING DELAYS/DOSE MODIFICATIONS

*Treatment plans should explicitly identify when treatment (typically dose) modifications are appropriate. Treatment modifications/dosing delays and the factors predicating treatment modification should be explicit and clear. If dose modifications or treatment delays are anticipated, please provide a dose de-escalation schema.*

*The following format for an orally available agent is provided as an example and should be modified as appropriate for this protocol.*

*If there is an* ***agent-specific protocol template*** *available from CTEP, please refer to it for the most current dose modification guidelines for that agent.*

|  |  |
| --- | --- |
| **Dose Level** | ***[Agent Name]* Dose** |
| -2 | *XX mg, schedule* |
| -1 | *XX mg, schedule* |
| 0 | *XX mg, schedule* |
| +1 | *XX mg, schedule* |
| +2 | *XX mg, schedule* |
| +3 | *XX mg, schedule* |

***Note:*** *All treatment modifications must be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose.*

*For combination studies, dose modifications/treatment delays for [Drug 1, 2, etc.] and [Other Agent(s)] may be presented separately or together, as appropriate. Use of a table format is recommended if applicable.*

*Below are dose modification tables for the following adverse events: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. Please use as appropriate. In addition, for your convenience, a blank dose modification table has been provided. Note in the text that if a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.*

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

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

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

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

| **Thrombocytopenia** | **Management/Next Dose for *[Agent Name]*** | **Management/Next Dose for *[Agent Name]*** |
| --- | --- | --- |
| ≤ Grade 1 | No change in dose | No change in dose |
| Grade 2 | Hold until ≤ Grade 1. Resume at same dose level. | Hold until ≤ Grade 1. Resume at same dose level. |
| Grade 3 | Hold\* until < Grade 2. Resume at one dose level lower, if indicated.\*\* | Hold\* until < Grade 2. Resume at one dose level lower, if indicated.\*\* |
| Grade 4 | Off protocol therapy | Off protocol therapy |
| \*Patients requiring a delay of >2 weeks should go off protocol therapy.  \*\*Patients requiring > two dose reductions should go off protocol therapy. | | |
| *Insert any recommended management guidelines, if appropriate.* | | |

*Example of Dose Modification Table:*

| ***Event*** | **Management/Next Dose for *[Agent Name]*** | **Management/Next Dose for *[Agent Name]*** |
| --- | --- | --- |
| ≤ Grade 1 | *Insert appropriate management guidelines in this column.* | *Insert appropriate management guidelines in this column.* |
| Grade 2 |  |  |
| Grade 3 |  |  |
| Grade 4 |  |  |
| \**Footnote any relevant guidelines regarding how long a delay in therapy is allowed before patients should go off protocol therapy*  \*\**Footnote any relevant guidelines regarding how many dose reductions are allowed before patients should go off protocol therapy.* | | |
| *Insert any recommended management guidelines, if appropriate.* | | |

# PHARMACEUTICAL and/or IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 10.1.

*Sections provided below should be used or deleted as necessary. Adjust the heading levels as appropriate (*e.g.*, if only one agent is included in the protocol template, the subsections below can be deleted, and the pharmaceutical information for that agent inserted directly under heading 8.1). Include a subsection regarding* ***Availability, Ordering,*** *and* ***Accountability*** *for each agent included in the protocol.*

## Insert Research Drug or Agent Name Pharmaceutical Information)

* + 1. *Insert Drug/Agent Name*

*Insert pharmaceutical and/or imaging information for Research Drug/Agent #1 here.*

*For CIP agents, include reference to the current Investigator’s Brochure, and include appropriate Dosimetry, Quality Assurance, Quality Control, and Storage information from the Investigator’s Brochure and/or supplier.*

**Availability**

*[Drug/Agent #1]* is an investigational agent supplied to investigators by *INSERT DRUG SUPPLIER INFORMATION.*

* + 1. *Drug/Agent #2*

*If only a single CTEP and/or CIP IND Agent will be used in the trial, this section and the text below should be deleted.*

**Availability**

*[Drug/Agent 2]* is an investigational agent supplied to investigators by *INSERT SUPPLIER*

* + 1. Agent Ordering and Agent Accountability
       1. *Insert how Drug/Agent can be ordered*
       2. Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received using institutional Drug Accountability Record (DARF) or other methods of recording Store and maintain separate Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.
    2. Investigator Brochure Availability

The current versions of the IBs will be accessible to site investigators and research staff.

## Other Investigational Agent(s)

*If there are no other investigational agent(s) in this study, this section and the instructions below should be deleted.*

*A separate pharmaceutical section is needed for each investigational agent containing at least the following information, available from the appropriate Investigator’s Brochure:*

***Product description****: Include the available dosage forms, ingredients, and packaging, as appropriate. Also state the agent's supplier.*

***Solution preparation*** *(how the dose is to be prepared): Include reconstitution directions and directions for further dilution, if appropriate.*

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

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

***Route of administration:*** *Include a description of the method to be used and the rate of administration, if applicable. For example, continuous intravenous infusion over 24 hours, short intravenous infusion over 30-60 minutes, intravenous bolus,* etc. *Describe any precautions required for safe administration.*

***Agent Ordering:*** *Include instructions for agent procurement processes.*

*For imaging agents, include reference to the current Investigator’s Brochure, and include appropriate Dosimetry, Quality Assurance, Quality Control, and Storage information from the Investigator’s Brochure and/or supplier.*

## Commercial Agent(s)

*If there are no commercial agent(s) in this study, this section and the instructions below should be deleted.*

*A separate pharmaceutical section is needed for each agent containing at least the following information, available in the manufacturer's current package insert:*

***Product description****: Include any dosage form(s), ingredients, and packaging applicable to the protocol. Also, state the agent's supplier or state that it is commercially available.*

***Solution preparation*** *(how the dose is to be prepared): Investigators may refer the reader to the package insert for 'standard' preparation instructions. If the agent is to be prepared in a 'non-standard' or protocol-specific fashion, the reconstitution directions and instructions for further dilution must be included. Appropriate storage and stability information should be included to support the method of preparation.*

***Route of administration:*** *Include a description of the method to be used and the rate of administration, if applicable. For example, continuous intravenous infusion over 24 hours, short intravenous infusion over 30-60 minutes, intravenous bolus,* etc. *Describe any precautions required for safe administration.*

***Agent Ordering:*** *Include instructions for agent procurement processes. If agent is being purchased, state that the agent is commercially available. Or, if commercial agent is being provided for the study, the supplier should be identified.*

*For imaging agents, include reference to the current Investigator’s Brochure, and include appropriate Dosimetry, Quality Assurance, Quality Control, and Storage information from the Investigator’s Brochure and/or supplier.*

# STATISTICAL CONSIDERATIONS

## Study Design/Endpoints

*Please specify the study design and primary endpoints. Include information on how toxicity will be graded and reported, and state that all patients who receive any amount of the study drug will be evaluable for toxicity. Precisely define the dose escalation scheme and MTD definition (or refer to the section where they are defined). Alternative dose escalation designs may be used (*e.g.*, accelerated titration), but should be fully described in the protocol. An example of an alternative dose escalation schedule can be found on the following website (*[*http://linus.nci.nih.gov/~brb/Methodologic.htm*](http://linus.nci.nih.gov/~brb/Methodologic.htm)*)*. *If an optimal biologic dose will be determined in place of or in addition to the MTD, precisely define how this will be done.*

*Any phase 1, phase 1 combination, or phase 2 study that proposes the use of an expansion cohort, regardless of size or phase, must include a statistical plan for analysis and a stopping rule for futility where appropriate as part of the statistical analysis plan. Types of expansion cohorts include cohorts for dose/schedule refinement, a variety of tumor types, a variety of molecularly-defined subsets, or other drug combinations. Where appropriate, eligibility criteria should be provided and addressed in the informed consent document. A rationale for the inclusion of specific tumor types should be provided. A sample size justification is needed. Defined endpoints for efficacy and futility should be part of the statistical analysis plan.*

*For recommendations regarding Phase 1 studies, please see the following reference:*

*Ivy SP, L Siu, E Garrett-Mayer, and L Rubinstein. (2010). Approaches to phase I clinical trial design focused on safety, efficiency, and selected patient populations: A report from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. Clin Cancer Res. 16(6):1726.*

*URL:* [*http://clincancerres.aacrjournals.org/content/16/6/1726.abstract*](http://clincancerres.aacrjournals.org/content/16/6/1726.abstract)

*For recommendations regarding Phase 2 studies, please see the following reference:*

*Seymour L, SP Ivy, D Sargent, et al. (2010). The design of phase II clinical trials testing cancer therapeutics: Consensus recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. Clin Cancer Res. 16(6):1764.*

*URL:* [*http://clincancerres.aacrjournals.org/content/16/6/1764.abstract*](http://clincancerres.aacrjournals.org/content/16/6/1764.abstract)

*Additional recommendations for phase 1 and 2 trials can be found on the CTEP website:* [*http://ctep.cancer.gov/*](http://ctep.cancer.gov/)

## Sample Size/Accrual Rate

*Please specify the planned sample size and accrual rate (*e.g.*, patients/month)*. *Add information regarding advanced imaging sample size as appropriate.*

*In accordance with NIH policy, the inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The Research Plan should describe the composition of the proposed study population in terms of sex/gender, race, and ethnicity, and provide a rationale for selection of subjects. Please see* [*http://grants.nih.gov/grants/funding/phs398/phs398.pdf*](http://grants.nih.gov/grants/funding/phs398/phs398.pdf)*.*

*The NCI suggests that the accrual targets be based on data from similar trials completed by your organization during the previous 5 years. It is hoped that the accrual targets will resemble the gender, ethnic, and racial composition of the U.S. population as closely as possible.*

## Stratification Factors

*Please specify any planned patient stratification factors. Indicate whether dose escalation and MTD determination will be done for each stratum individually.*

## Analysis of Secondary Endpoints

*If secondary endpoints are included in this study, please specify how they will be analyzed. In particular, brief descriptions should be given of analyses of pharmacokinetic, biologic, and correlative laboratory endpoints.*

*If responses are reported as a secondary endpoint, the following criteria should be used. Every report should contain all patients included in the study. For the response calculation, the report should contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. However, a response rate analysis based on a subset of patients must explain which patients were excluded and for which reasons. It is preferred that 95% confidence limits are given.*

## For phase 2 protocols only: Reporting and Exclusions

* + 1. Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with *[Drug/ Agent(s)].*

* + 1. Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

# ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

## Listing of Known Risks of *Insert Drug Name or Research Intervention*

*In this section please provide a listing of* ***all*** *known risks of the research drug/device/intervention – reference the IB or package insert as needed. If a risk is listed here then if the event does occur, it will be considered to be expected and will NOT require prompt reporting to the IRB or FDA or UC DSMB even if it is serious and related to study participation. Having a complete listing here also ensures the consent form is accurately written and patients are fully informed of all risks of participation.*

*For interventions without an IB – please state in the PI’s opinion the potential common risks of the intervention.*

## Adverse events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug/intervention and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The severity (grade) of an adverse event may be determined by a study coordinator using the CTCAE Version 5.

The causal relationship (attribution) to study drug/device/intervention is determined by a study physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

1. Unrelated – The AE is clearly NOT related to the study intervention
2. Unlikely – The AE is doubtfully related to the study intervention
3. Possible – The AE may be related to the study intervention
4. Probable – The AE is likely related to the study intervention
5. Definite – The AE is clearly related to the study intervention

The expectedness of the occurrence of an adverse event is determined by a study physician and should be used to help determine whether prompt reporting requirements to regulatory authorities (IRB, FDA etc…) are required are required (such as when the AE is an SAE).

1. Expected – An adverse event is expected if it is described as an anticipated risk in the Investigator Brochure (IB) and described within this protocol as a known adverse event.
2. Unexpected – If an adverse event is not described within the IB, or within this protocol or consent form as an expected risk to subjects then the AE will be considered to be unexpected.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

## Serious Adverse events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

1. Results in Death
2. Is Life Threatening
3. Requires inpatient or prolonged hospitalization
4. Results in persistent or significant disability or incapacity
5. Results in a congenital abnormality or birth defects
6. Is any other serious medical condition in the opinion of the PI

The following are NOT considered to be SAEs for the purposes of this protocol:

1. Elective surgery, planned prior to signing consent.
2. Admissions per protocol for planned medical/surgical procedures
3. Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)

## Serious Adverse Events Collection & Reporting

All Serious Adverse Events (SAEs) that occur following the subject’s written consent and within 30 days after the subject’s last dose of study drug should be reported using a MedWatch form within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: <http://www.accessdata.fda.gov/scripts/medwatch/>. SAEs considered by the Investigator to be related to study medication will be reported regardless of the timeframe from last dose of protocol therapy. UCCC CTO workflows must be followed when collecting and reporting all SAEs.

The study team will report SAEs to the UCCC CTO and IRB and FDA according to their respective prompt reporting timeframes.

OR

All Serious Adverse Events (SAEs) that occur after consent and within 30/60/90 days after the subject’s end of treatment or before initiation of a new anti-cancer treatment must be collected. SAEs considered by the Investigator to be related to a study intervention and unexpected will be reported regardless of the timeframe from last study treatment. SAEs must be followed to resolution or stabilization.

* All SAEs must be collected and recorded following current UCCC CTO workflows (e.g., electronic AE logs in EMR).
* All SAEs must be reported within 24 hours of the study team becoming aware of the initial SAE or any follow-up information regarding the SAE to the PI and UCCC CTO regulatory and quality assurance staff per UCCC workflows (e.g., SAE alert emails, entry into CTMS and EDC).
* The study team must report SAEs to the UC IRB and/or FDA according to their respective prompt reporting timeframes. If reporting to the FDA is determined to be required the FDA’s MedWatch Form for voluntary reporting must be completed. SAEs must be recorded within the study EDC and UCCC CTO CTMS.

## Adverse Event Collection and Reporting

The collection of AE information should begin at initiation of study drug. All adverse events regardless of attribution should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Concomitant illnesses that existed before entry into the study are to be documented as medical history and graded, but will not be considered AEs unless the illness worsens after initiating protocol therapy.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented but not reported as an SAE. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient’s disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All AEs must be collected and recorded following current UCCC CTO workflows.

## Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

## Adverse Event Grading

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

## Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented in REDCap. Any pregnancy occurring in a patient or patient’s partner from the time of consent to 180 days after the last dose of study drug must be reported and then followed for outcomes. Newborn infants should be followed until 30 days old.

The Sponsor Institution has the responsibility to monitor the outcome of all pregnancies reported during this study.

An elective abortion without complications should not be regarded as an AE, however, it should be reported as the outcome to the pregnancy. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

## Contraception/Birth Control

Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation. Effective birth control is considered to be:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

* Oral route, Intravaginal route or Transdermal route

1. Progestogen-only hormonal contraception associated with inhibition of ovulation

* Oral, Injectable, or Implantable

1. Intrauterine device
2. Intrauterine hormone-releasing system
3. Bilateral tubal occlusion
4. Vasectomized partner
5. Sexual abstinence

## Breast Feeding

Participants must not breast-feed while receiving protocol therapy and for 180 days following the last dose of protocol therapy

## 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.

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

## Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

# STUDY CALENDAR

***Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate to match the protocol.***

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done <4 weeks prior to the start of therapy. In the event that the patient’s condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Milestone (screening, tx, follow-up, surgery or specific cycles)** | **Screen** | **C1** | **C1** | **C1** | **C2** | **C2** | **C2** | **C3** | **C3** | **C3** | **C4-8** | **End of Tx** | **30 day Safety** | **Long term follow-up** |
| **Time point for milestone (weeks or days, or months)** | **-28 days** | **Wk**  **1** | **Wk 2** | **Wk 3** | **Wk 4** | **Wk 5** | **Wk 6** | **Wk 7** | **Wk 8** | **Wk 9** |  | **Wk 11** | **30 D post end tx** | **Every 6 monthsa** |
| **Window (+/- 1 day, 1 week 3 months etc.. – use to avoid deviations)** | **+/-** | **+/-** | **+/-3 Day** | **+/-** | **+/-** | **+/-** | **+/-** | **+/-** | **+/-** | **+/-** | **+/-** | **+/-** | **+/- 7 days** | **+/- 4 weeks** |
| *[Study Drug/Agent]* |  | X |  |  | X |  |  | X |  |  | X |  |  |  |
| *[Other Agent(s)]* |  | X | X |  | X | X |  | X | X |  | X | X |  |  |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Randomization (if applicable) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Con meds | X | X | X |  |  |  |  |  |  |  |  |  |  |  |
| Adverse events |  | X | X |  |  |  |  |  |  |  |  |  |  |  |
| Full Physical exam | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Directed Physical exam |  | X | X |  |  |  |  |  |  |  |  |  |  |  |
| Vital signs | X | X | X |  |  |  |  |  |  |  |  |  |  |  |
| Height | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Weight | X | X | X |  |  |  |  |  |  |  |  |  |  |  |
| Performance statusb | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CBC w/diff, plts | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum chemistryc | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| EKG (as indicated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ADD IN ALL OTHER LAB TESTS from TABLE 5 for ex: Lactase, B-12, C-peptide etc…each gets own row or footnote them. |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Imaging (specify if CT, CT with contrast, MRI or other) | X |  | X |  |  |  |  |  |  |  |  |  |  |  |
| Medication Diary – **you MUST include if Oral drug is being used** | X | X | X |  |  |  |  |  |  |  |  |  |  |  |
| Pregnancy testd | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Advanced imaging events,  as appropriate* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Other tests, as appropriate* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Other correlative studies – make separate rows for blood, archival tissue or fresh tissue if one being missed make the others not needed note this in footnotes* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| You should use the footnotes to note when a procedure is at a different timepoint than indicated in the calendar’s window; to list out specific lab tests; to give any clarification necessary to ensure the study activities are performed accurately (e.g., pre-treatment blood correlatives must be collected only after eligibility is confirmed but before treatment and if not able to collect then no additional blood correlatives should be collected.  You can create a footnote here by clicking on this icon and then adding the corresponding letter to this section.    b: Note: Performance status evaluations are based on a 4 week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.  c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.  d: Pregnancy test for women of childbearing potential. | | | | | | | | | | | | | | |

# MEASUREMENT OF EFFECT

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

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

## Antitumor Effect – Solid Tumors

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

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

* + 1. Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *[CTEP and/or CIP IND Agent(s)]*.

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

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

* + 1. Disease Parameters

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

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

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

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

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

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

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

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

* + 1. Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* + 1. Response Criteria
       1. Evaluation of Target Lesions

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

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

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

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

* + - 1. Evaluation of Non-Target Lesions

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

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

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

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

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

* + - 1. Evaluation of Best Overall Response

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

**For Patients with Measurable Disease (*i.e.*, Target Disease)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Overall Response when Confirmation is Required\*** |
| CR | CR | No | CR | ≥4 wks. Confirmation\*\* |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. Confirmation\*\* |
| CR | Not evaluated | No | PR |
| PR | Non-CR/Non-PD/not evaluated | No | PR |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥4 wks. from baseline\*\* |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD\*\*\* | Yes or No | PD |
| Any | Any | Yes | PD |
| * See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.   \*\* Only for non-randomized trials with response as primary endpoint.  \*\*\* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.  Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration.”* Every effort should be made to document the objective progression even after discontinuation of treatment. | | | | |

**For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)**

|  |  |  |
| --- | --- | --- |
| **Non-Target Lesions** | **New Lesions** | **Overall Response** |
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD\* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |
| * ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised | | |

* + 1. Duration of Response

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

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

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

* + 1. Progression-Free Survival

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

* + 1. Response Review

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

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

* + 1. Definitions

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

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

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

* + 1. RECIST 1.1 Response and Evaluation Endpoints

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

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

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

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

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

* + 1. Response Criteria

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

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

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

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

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

| **Integration of target, non-target, and new lesions into response assessment** | | | | |
| --- | --- | --- | --- | --- |
| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Response For This Category Also Requires** |
| **Target lesions ± non target lesions** | | | | |
| CR | CR | No | CR | Normalization of tumor markers, tumor nodes <10 mm |
| CR | Non-CR/non-PD | No | PR | Normalization of tumor markers, tumor nodes <10 mm |
| CR | Not all evaluated | No | PR |  |
| PR | Non-PD/not all evaluated | No | PR |  |
| SD | Non-PD/not all evaluated | No | SD | Documented at least once ≥4 weeks from baseline |
| Not all evaluated | Non-PD | No | NE |  |
| PD | Any | Any | PD |  |
| Any | PD | Any | PD |  |
| Any | Any | Yes | PD |  |
| **Non target lesions ONLY** | | | | |
| No Target | CR | No | CR | Normalization of tumor markers, tumor nodes <10 mm |
| No Target | Non-CR/non-PD | No | Non-CR/ non-PD |  |
| No Target | Not all evaluated | No | NE |  |
| No Target | Unequivocal PD | Any | PD |  |
| No Target | Any | Yes\* | PD |  |
| Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.  \*Investigators should record all new lesions. If the new lesion is felt to be equivocal, treatment may be continued pending further assessments. | | | | |

* + 1. iRECIST Response Assessment

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

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

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

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

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

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

New lesions:

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

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

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

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

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

| **iRECIST best overall response (iBOR)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **TPR 1** | **TPR 2** | **TPR 3** | **TPR 4** | **TPR 5** | **iBOR** |
| iCR | iCR, iPR, iUPD, NE | iCR, iPR, iUPD, NE | iUPD | iCPD | iCR |
| iUPD | iPR, iSD, NE | iCR | iCR, iPR, iSD, iUPD, NE | iCR, iPR, iSD, iUPD, iCPD, NE | iCR |
| iUPD | iPR | iPR, iSD, iUPD, NE | iPR, iSD, iUPD, NE, iCPD | iPR, iSD, iUPD, NE, iCPD | iPR |
| iUPD | iSD, NE | PR | iPR, iSD, iUPD, NE | iPR, iSD, iUPD, iCPD, NE | iPR |
| iUPD | iSD | iSD, iUPD, NE | iSD, iUPD, iCPD, NE | iSD, iUPD, ICPD, NE | iSD |
| iUPD | iCPD | Anything | Anything | Anything | iCPD |
| iUPD | iUPD | iCPD | Anything | Anything | iCPD |
| iUPD | NE | NE | NE | NE | iUPD |
| Table assumes a randomized study where confirmation of CR or PR is not required.   * NE = not evaluable that cycle. * Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation. * For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation. | | | | | |

* + 1. Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

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

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

* + 1. Methods of Measurement

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

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

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

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

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

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

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

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (*e.g.*, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or SD and PD.

## Antitumor Effect – Hematologic Tumors

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

## Other Response Parameters

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

# STUDY OVERSIGHT, DATA REPORTING & Regulatory

## Study Oversight

This protocol is monitored at several levels, as described in this section.  The UC Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events.  The UC Principal Investigator has access to the data at all times through the study EDC, REDCap.

This study will also be reviewed in accordance with the UCCC CTO’s SOPs, Policies and Guidance which may include periodic routine or for cause internal auditing. The study team must adhere to the current policies, SOPs, guidance and workflows of the UCCC CTO in the conduct of this protocol.

All study investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via REDCap and timely reporting of adverse events. This includes timely review of data collected on electronic CRFs submitted via REDCap as well as review of any source documentation collected locally.

This study will also be reviewed in accordance with the enrolling institution’s data safety monitoring plan.

## Data Reporting

Data collection and storage at the University of Cincinnati will be managed by the University of Cincinnati Cancer Center, Clinical Trials Office (UCCC CTO). The UCCC CTO will maintain storage of all clinical data in accordance with federal guidelines and GCP. Data will be entered into the secure study EDC, REDCap and into the CTO CTMS. All hardcopies of data will be securely maintained (in a locked room or cabinet) and will only be accessible to members of the study team or UCCC CTO personnel.

Study data collected at sub-sites should be stored securely per local policies, and be made accessible to UC as required.

* + 1. Data Safety Monitoring Board

Any new significant finding that may affect the patient’s willingness to continue in the study will be shared with patients. Immediately after the study is approved and before the first patient is enrolled, investigators will meet, develop and finalize all measurements/variables for the study. Each patient, once enrolled, will be provided a unique ID for the study. Personal information, such as name, SSN, address, phone number and DOB, will be de-identified whenever possible from study records. Confidentiality will be maintained during the phases of the trial including preparation of interim results, review, and response to internal auditing or DSMB or IRB recommendations.

Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety.

Study progress will be monitored regularly by the UCCC Data Safety Monitoring Board (DSMB). Membership consists of persons independent of, and without any conflicts of interest with, this trial. The DSMB includes experts in the fields of relevant clinical expertise (oncology) and biostatistics.

It is the responsibility of the UC Investigator to ensure that the DSMB is apprised of all new safety information relevant to the study. Study progress & safety information will be prepared by the DSMB Coordinator with input from the UC PI as to the current status of the trial. This compiled information presented to the DSMB will include: a narrative summary from the UC PI as to trial progress and identification of any trends of significance or explanation of any SAEs or other safety related events; the accrual rate with projected completion date for the accrual phase; exclusion rates and reasons when relevant; pretreatment characteristics of patients accrued when relevant; and, the frequency and severity of adverse events.

The DSMB will function in an advisory capacity and recommendations/requests from the

DSMB will be reviewed by the UC investigator and promptly addressed.

The study data from participating sub-sites will be reviewed remotely via the study EDC RedCAP and in person by the Study Monitor as per the Clinical Monitoring Plan (Plan kept on file with UCCC CTO office).

## SMART IRB

This study will utilize the Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform (SMART IRB) master IRB reliance agreement to establish reliance arrangements with research sub-sites. Launched in 2016, SMART IRB is currently funded by the NIH Clinical and Translational Science Awards (CTSA) Program, grant number UL1TR002541-01S1. The platform serves as a roadmap for institutions to implement The National Institutes of Health (NIH) Policy on the Use of a Single Institutional Review Board for Multisite Research.

The UC IRB will perform initial review and continuing oversight of the protocol and research sites in accordance with the human subjects protection requirements of its FWA, the FWAs of relying IRBs, the federal regulations, and ethical principles referenced therein.

## Genomic Data Sharing Plan

*If genomic data will be studied, analyzed, collected, and stored in an NIH/NCI Genomic Data Biorepository (*e.g.*, dbGaP, other), please describe the genomic data sharing plan for this trial. Please refer to the NCI Genomic Data Sharing Policy at* [*http://www.cancer.gov/grants-training/grants-management/nci-policies/genomic-data*](http://www.cancer.gov/grants-training/grants-management/nci-policies/genomic-data) *for considerations regarding the sharing of data, protection of patient confidential information, and the provision of adequate information in the patient informed consent.*

*Remove this section if N/A*

## Incidental/Secondary Findings Disclosure Procedure

*Please provide any planned disclosure procedures for and incidental/secondary findings of germline and/or somatic mutations. Describe how the treating physician will be contacted, how patients will be informed (*e.g., *if a genetic counselor be present), and how research findings will be confirmed (*e.g., *Sanger sequencing).*

*Remove this section if N/A*

# REFERENCES

*Please provide the citations for all publications referenced in the text.*

PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez, JG. Conde, Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr;42(2):377-81.

PA Harris, R Taylor, BL Minor, V Elliott, M Fernandez, L O’Neal, L McLeod, G Delacqua, F Delacqua, J Kirby, SN Duda, REDCap Consortium, The REDCap consortium: Building an international community of software partners, J Biomed Inform. 2019 May 9 [doi: 10.1016/j.jbi.2019.103208]

# 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. |

# APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI’s Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).   Formulae:   |  |  |  | | --- | --- | --- | | **Race and Sex** | **Serum Creatinine (SCr), *µmol/L (mg/dL)*** | **Equation** | | **Black** |  |  | | Female | ≤62 (≤0.7) | GFR = 166 × (SCr/0.7)−0.329 × (0.993)Age | |  | >62 (>0.7) | GFR = 166 × (SCr/0.7)−1.209 × (0.993)Age | | Male | ≤80 (≤0.9) | GFR = 163 × (SCr/0.9)−0.411 × (0.993)Age | |  | >80 (>0.9) | GFR = 163 × (SCr/0.9)−1.209 × (0.993)Age | |  |  |  | | **White or other** |  |  | | Female | ≤62 (≤0.7) | GFR = 144 × (SCr/0.7)−0.329 × (0.993)Age | |  | >62 (>0.7) | GFR = 144 × (SCr/0.7)−1.209 × (0.993)Age | | Male | ≤80 (≤0.9) | GFR = 141 × (SCr/0.9)−0.411 × (0.993)Age | |  | >80 (>0.9) | GFR = 141 × (SCr/0.9)−1.209 × (0.993)Age |   SCr in mg/dL; Output is in mL/min/1.73 m2 and needs no further conversions. |
| 1. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).   175 x SCr–1.154 × age–0.203 × 0.742 (if female) × 1.212 (if black)  Output is in mL/min/1.73 m2 and needs no further conversions. |
| 1. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).     Followed by conversion to a value normalized to 1.73 m2 with the patient’s body surface area (BSA). |

References

1. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al*. (2009). A new equation to estimate glomerular filtration rate. *Ann Inter Med*. 150:604-612.
2. Levey, A.S., J. Coresh, T. Greene, *et al*. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 145:247-254.
3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.