**Specific Instructions for the Use of Protocol Templates for Organ Dysfunction Studies**

The goal of an organ dysfunction study is to define the dose of an agent associated with an acceptable toxicity profile and measurable pharmacokinetic parameter(s) in patients whose impaired organ function may alter the absorption and disposition (pharmacokinetics) as well as the efficacy and safety (pharmacodynamics) of that agent. Ideally, the pharmacokinetic parameter(s) identified will correlate with the clinical effects of an agent. The target level of the chosen parameter(s) could thus serve to guide optimal dosing for a given patient. Organ dysfunction studies are designed to evaluate toxicity and to measure pharmacokinetic and pharmacodynamic parameters in each of up to five cohorts of patients with varying degrees of organ dysfunction at each dose of the agent administered.

Investigators planning to conduct studies in cancer patients with impaired hepatic or renal function should consider the following points:

1. **FDA Guidance**

The investigator is advised to refer to the guidance provided by the Food and Drug Administration (FDA) on conducting studies in patients with organ dysfunction when planning their study. While not specifically written for neoplastic diseases, the following documents should be consulted:

Hepatic dysfunction: “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” (posted 5/20/2003) is available as a PDF document (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>).

Renal dysfunction: “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” (posted 5/14/1998) is available as a PDF document (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072127.pdf>).

This template is based on the final 1998 guidance referenced above. A nonbinding, draft update was posted for comment on 3/22/2010 at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> .

1. **Extensive PK Sampling**

Investigators planning to conduct studies in these special groups of patients should be prepared to conduct extensive pharmacokinetic (PK) sampling for the agent in question as well as its active metabolites to provide meaningful results that will lead to appropriate dosing recommendations. Identification of PK parameter(s) that correlate with an acceptable toxicity profile and which can then guide future dose recommendations (*e.g.,* AUC when used as the target level for carboplatin dosing) is a goal of these studies. Because relatively small patient cohorts are indicated, detailed PK measurements become especially important. Once the PK parameter(s) and the target level have been identified in a small study cohort (6 patients), an expanded cohort of 12-15 patients should be treated using the selected parameter(s) and target level with extensive PK measurements to validate use of the parameter(s) to guide dosing.

1. **CYP450 Metabolic Interactions**

The possibility that enzymatic activity of the CYP450 system may affect the agent of interest or its metabolites should be considered as well as the effect of concomitant medications. Investigators should also consider the possibility that these metabolic products could be excreted via an alternative route rather than the known primary route of elimination. The investigator should be prepared to exclude all medications that may affect the activity of CYP450 isoenzymes that interact with the study agent, as well as any other potential sources of drug-drug interactions (*e.g.*, P-glycoprotein, *etc.*)

1. **Combination Regimens**

If a study using a combination of agents is under consideration, the investigator is strongly advised to consult with the FDA on an appropriate design prior to drafting the protocol. Some of the relevant issues that must be addressed include (1) the choice of regimen and (2) the need for extensive sampling and PK measurements to isolate and identify any interactions between the agents administered.

1. **Data Capture**

Investigators who conduct an organ dysfunction study should plan to make the raw data from their trial available to the FDA in the final study report. Data of interest include those data used to estimate hepatic function and to calculate the Child-Pugh Classification (CPC; hepatic studies) or data used to estimate the creatinine clearance using the Cockcroft-Gault formula and to estimate the glomerular filtration rate using the MDRD formula (renal studies). In addition, the final study report should contain all pharmacokinetic, pharmacodynamic, clinical, and laboratory data from the trial as well as the case report forms.

**TEMPLATE INSTRUCTIONS**

The protocol template is a tool to facilitate rapid protocol development. It is not intended to supersede the role of the Protocol Chair in the authoring and scientific development of the protocol. It contains the “boilerplate” language commonly required in protocols submitted to CTEP. Content may be modified as necessary to meet the scientific aims of the study and development of the protocol. Much of the formatting is needed for electronic submission of the protocol to the FDA and should not be changed unless necessary.

**Note:** This template contains language specific for Experimental Therapeutics Clinical Trials Network (“**ETCTN**”) trials as well as for CTEP-sponsored trials coordinated outside of the ETCTN or other Network/Cooperative Groups (“**Non-Network**,” which may include single-center or multi-center trials). Please take note of any instructional text in *italics,* emphasized with red highlighting, which notes where language specifically applies to “ **ETCTN** ” or “**Non-Network** ” trials. Please note that CTEP will designate your trial as either an ETCTN or Non-Network trial when the Letter of Intent (LOI) is approved. If your trial is designated as an ETCTN trial, then all ETCTN specific language must be retained in your protocol. Non-Network trials may delete language specific for ETCTN trials, and vice versa.

1. Each Protocol Template consists of two parts:

a. Protocol Submission Worksheet: available at

<http://ctep.cancer.gov/forms/docs/psw.docx>. This document contains prompts for required administrative information.

b. Main Body and Appendices of the protocol: attached below. This document provides standard language plus instructions and prompts for information.

Please note that the Informed Consent Template is provided as a separate document file.

2. The Protocol Submission Worksheet and Protocol/Informed Consent Template documents should be completed, and all documents (including the Appendices) should be submitted to CTEP for review. For protocol amendments a Summary of Changes should be provided as the first page (page i) of the document, as indicated in the template. The Summary of Changes must provide hyperlinks to the area referenced in the protocol or informed consent document.

3. All sections in the Protocol Template should be retained to facilitate rapid review. If not appropriate for a given study, please insert “Not Applicable” after the section number and delete unneeded text. 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 hepatic dysfunction protocols
* Blue highlighting – for renal dysfunction protocols
* **Grey** highlighting – language for ETCTN protocols that are using the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank) (formerly the ETCTN Biorepository) and/or National Clinical Laboratory Network (NCLN) resources.

4. All Protocol Template instructions and prompts are in *italics*. **As you complete the information requested, please delete the italicized text.**

5. Please note that the Protocol Template has built-in styles for headings levels 1-4 (Level 1 Heading – Level 4 Heading; see image below).

MS Word Style ribbon

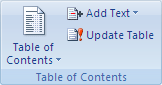
These heading styles will automatically update the Table of Contents (TOC) and convert to Bookmarks in a final PDF protocol document. **Please retain the heading styles.**

6. Before updating the TOC, please ensure that the **Title Page** is page 1 of the protocol. For any pages preceding it (*i.e.*, Summary of Changes) use alternative numbering (i, ii, iii, iv, … ). Use Section Breaks as necessary to preserve this numbering scheme.

7. To update the TOC in your protocol document:

MS Word 2007 or later

a. Under the **References** tab, in the **Table of Contents** group, click **Update Table**.



b. Click **Update entire table**.

MS Word 2003

a. Click the table of contents.

b. Press F9.

**Please do not edit the TOC manually.**

8. Please redline, highlight or underline new or modified text as this will facilitate rapid review.

9. Note that CTEP cannot accept MS Word files that:

* are read-only
* are password protected
* contain macros
* are saved with a file extension other than .doc (Word 2003) or .docx (Word 2007 onward)

10. For problems or questions encountered when using these documents (Protocol Submission Worksheet or Protocol/Informed Consent Template), please contact the CTEP Protocol and Information Office (PIO) by e-mail ([pio@ctep.nci.nih.gov](mailto:pio@ctep.nci.nih.gov)).

**SUMMARY OF CHANGES – Protocol**

For Protocol Amendment # to:

NCI Protocol #:

Local Protocol #:

NCI Version Date:

Protocol Date:

*Please provide a list of changes from the previous CTEP approved version of the protocol. The list shall identify by page and section each change made to a protocol document with hyperlinks to the section in the protocol document. All changes shall 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. |  |  |

*(Please retain the section break below, so that the Title Page is page “1” of the document.)*

**NCI Protocol #:** *Use the number assigned to the LOI by the NCI.*

**Local Protocol #:** *Please insert your local protocol # for this study.*

**ClinicalTrials.gov Identifier:** *[Insert ClinicalTrials.gov NCT#, if known, in the format “NCTxxxxxxxx”; otherwise, “TBD”]*

**TITLE:** A Phase 1 and Pharmacokinetic Single Agent Study of *[CTEP IND Agent]* in Patients with Advanced Malignancies and Varying Degrees of *[Hepatic/Renal]* Dysfunction

*Use Simplified Disease Classification (SDC) terminology for study disease. Please refer to the CTEP website (*[*http://ctep.cancer.gov/protocolDevelopment/codes\_values.htm*](http://ctep.cancer.gov/protocolDevelopment/codes_values.htm)*) for a complete list of SDC disease terms.*

**Corresponding Organization:** *Use this field for*  ***ETCTN***  *trials (Non-Network trials should delete). This is the name of the Lead Academic Organization (LAO) submitting the protocol. Please select from the table of LAOs below and please include the CTEP code.*

**Coordinating Center:** *Use this field for*  ***Non-Network***  *trials (ETCTN trials should delete). Multicenter trials can only list one organization/ institution as the Coordinating Center.*

**Principal Investigator:** *Name*

*Institution*

*Address*

*Address*

*City, State/Province, Zip Code/Postal Code, Country*

*Telephone*

*Fax (optional)*

*e-mail address*

**Translational PI:** *Name*

*Institution*

*Address*

*Address*

*City, State/Province, Zip Code/Postal Code, Country*

*Telephone*

*Fax (optional)*

*e-mail address*

***A study can have only one Principal Investigator. The Principal Investigator must be a physician and is responsible for all study conduct.*** *Please refer to the Investigator's Handbook on the CTEP website for a complete description of the* ***Principal Investigator's*** *responsibilities (*[*http://ctep.cancer.gov/investigatorResources/default.htm#Investigators\_handbook*](http://ctep.cancer.gov/investigatorResources/default.htm#Investigators_handbook)*).*

***The translational PI will be a co-primary PI on any ETCTN study where biomarker use is an integral or integrated part of the study****. The translational PI will have oversight and be responsible for coordinating all biomarker characterization and analysis. The translational PI and clinical PI will collaborate on the biomarker and endpoint analysis for the clinical investigation.*

*ETCTN trials involving a biopsy procedure must include an Interventional Radiologist as part of the study team.*

***All study personnel listed on the title page must have a current registration on file with CTEP.*** *Refer to section 4.1 for document requirements for each registration type and system access requirements. Failure to register all study personnel on the title page could delay protocol approval. If you are unsure of an individual’s registration status, please contact the Pharmaceutical Management Branch, CTEP at (240) 276-6575 or by e-mail at* [[RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov)](mailto:PMBRegPend@ctep.nci.nih.gov)*.*

*The protocol title page of the*  ***ETCTN***  *Rostered Model template lists all grantees that may potentially participate on an ETCTN protocol.* ***It is the responsibility of the Corresponding Organization to list the LAOs that will be participating on this study within the table below. Please contact PIO (***[***PIO@ctep.nci.nih.gov***](mailto:PIO@ctep.nci.nih.gov)***) for further instruction and guidance regarding the listing of participating LAOs.*** *Additional Non-ETCTN single institution participants should be added under “Non-Member Collaborators” according to the formatted example. Additional Non-ETCTN rostered organization participants (*e.g.*, ALLIANCE, ECOG-ACRIN, NRG, SWOG, COG, CCTG, CITN, BMTCTN, ABTC, PBTC, AMC, COGC) should be added under “Participating Organizations” as indicated below.*

**Participating Organizations** *(Only the participating LAOs should be listed.)*

|  |
| --- |
| **LAO-11030** / University Health Network Princess Margaret Cancer Center LAO |
| **LAO-CA043** / City of Hope Comprehensive Cancer Center LAO |
| **LAO-CT018** / Yale University Cancer Center LAO |
| **LAO-MA036** / Dana-Farber - Harvard Cancer Center LAO |
| **LAO-MD017** / JHU Sidney Kimmel Comprehensive Cancer Center LAO |
| **LAO-OH007** / Ohio State University Comprehensive Cancer Center LAO |
| **LAO-PA015** / UPMC Hillman Cancer Center LAO |
| **LAO-TX035** / University of Texas MD Anderson Cancer Center LAO |
| **LAO-NCI** / National Cancer Institute LAO |
| *Other Participating Rostered Organization #1 (*e.g.*, ALLIANCE, ECOG-ACRIN, NRG, SWOG, COG, CCTG, CITN, BMTCTN, ABTC, PBTC, AMC, or COGC; list one organization per row; add more rows as necessary)* |

**Non-Member Collaborators** *(additional individual participating sites within an ETCTN trial that are not members of a participating rostered organization)*

|  |  |
| --- | --- |
| *Institution #1 (non-rostered institution; insert more rows below as necessary for additional institutions; please include the CTEP Institution Code, which can be found at* [*http://ctep.cancer.gov/protocolDevelopment/codes\_values.htm*](http://ctep.cancer.gov/protocolDevelopment/codes_values.htm)*)*  *Name*  *Address* | *Investigator #1*  *Name*  *Telephone*  *Fax*  *E-mail address*  *Investigator #2*  *Name*  *Telephone*  *Fax*  *E-mail address*  *Investigator #3*  *Name*  *Telephone*  *Fax*  *E-mail address* |

*If this study includes an investigational agent supplied by the NCI Division of Cancer Treatment and Diagnosis and will involve a Canadian institution(s), a Clinical Trials Application (CTA) will need to be submitted to Health Canada for their participation in the study. A Canadian investigator should be designated to be responsible for preparing and submitting the CTA to Health Canada for the Canadian institution(s). Procedures and forms for preparing and submitting a CTA to the Canadian HPFB are available at* [*http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta\_application-eng.php*](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_application-eng.php)*. A copy of the “No Objection” letter must be forwarded to the Pharmaceutical Management Branch at* [*PMBAfterHours@mail.nih.gov*](mailto:PMBAfterHours@mail.nih.gov) *when available.*

**Interventional Radiologist:****Statistician:**

*(if applicable) (if applicable)*

*Name Name*

*Address Address*

*Address Address*

*Telephone Telephone*

*Fax Fax*

*e-mail address e-mail address*

**Study** **Coordinat****or:****Responsible Research Nurse:**

*(if applicable) (if applicable)*

*Name Name*

*Address Address*

*Address Address*

*Telephone Telephone*

*Fax Fax*

*e-mail address e-mail address*

**Responsible Data Manager:**

*Name*

*Address*

*Address*

*Telephone*

*Fax*

*e-mail address*

*Please list all agents and their suppliers in the fields below, including any imaging agents. “Supplier” is defined as the entity that provides the clinical supply of the agent.  If the agent is purchased through commercial sources, then please mark supplier as “commercial”.*

**NCI-Supplied Agent(s):** *[Agent Name and NSC #]*

**Other Agent(s):** *[Agent Name, NSC # (if applicable), and Supplier]*

*Below, please describe the IND Status of this study by choosing IND #/Sponsor* ***OR*** *Exemption from IND requirements, making sure to delete the inapplicable field(s).*

**IND #:** *[Enter the # of the IND under which this study will be performed. Enter “TBD” if an IND # is not yet available.]*

**IND Sponsor:** *[If this study is being conducted under an IND sponsored by CTEP, then enter “NCI DCTD/CTEP or DCTD/CTEP”. If this is solely an imaging study and is to be conducted under a CIP IND, then enter “Cancer Imaging Program, NCI”]*

*OR*

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

*If an IDE is not applicable to this study, then please delete the following fields (IDE #, IDE Sponsor, Device Name):*

**IDE #:** *[Investigational Device Exemption #]*

**IDE Sponsor**:

**Device Name:** *[This can include investigational* in vitro *diagnostics, which are regulated as devices]*

**Protocol Type / Version # / Version Date:** *[Type\* / Version # / Version Date]*

*\*Protocol types: Original, Revision, or Amendment*

# SCHEMA

***[Hepatic only]* LIVER DYSFUNCTION GROUPS**

Patients entering this study will be stratified into five groups or cohorts (A: normal, B: mild dysfunction, C: moderate dysfunction, D: severe dysfunction) according to their hepatic function as outlined in the following table:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group**  **Liver Function** | **Group A**  **Normal** | **Group B**  **Mild** | **Group C**  **Moderate** | **Group D**  **Severe** |
| **Total**  **Bilirubin** | ≤ ULN | B1: ≤ ULN  B2: >1.0× – 1.5× ULN | >1.5× – 3× ULN | >3× ULN |
| **SGOT/AST** | ≤ ULN | B1: > ULN  B2: Any | Any | Any |

**INVESTIGATIONAL AGENT**

*Please state route and schedule of Study Agent administration, and enter exact doses for each dose level and group in the table below. (For example, “Agent XXX is given intravenously as a 1-hour infusion on days 1, 3, and 5 of a 21-day cycle.”)*

*[CTEP IND Agent]* is given *[route, duration]* on *[day(s)]* of a *[#-day]* cycle.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Group A** | **Group B** | **Group C** | **Group D** |
| **Dose**  **Level** | **Normal liver function** (*units)*  \* | **Mild liver dysfunction** (*units)* \* | **Moderate liver dysfunction**  (*units)*  **\*** | **Severe liver dysfunction** (*units)* \* |
| **Level -1** |  |  |  |  |
| **Level 1** |  |  |  |  |
| **Level 2** |  |  |  |  |
| **Level 3** |  |  |  |  |
| **Level 4** |  |  |  |  |

***\* Doses are stated as exact dose in units (e.g., mg/m2, mcg/kg, etc.) rather than as a percentage.***

***\*\** (See Section 6.1.1 for the Group E dosing scheme.)**

Note: **This schema is not to be used for determining dosage for any individual patient. For specific dosing information, please refer to Sections 6 and 7.**

***[Renal only]* RENAL DYSFUNCTION GROUPS**

Patients entering this study will be stratified into up to five groups or cohorts (A: normal, B: mild dysfunction, C: moderate dysfunction, D: severe dysfunction, E: renal dialysis) according to their renal function based on their renal function estimate (eGFR, body-surface area (BSA)-indexed) as defined by the following table:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group**  **Renal Function** | **Group A**  **Normal** | **Group B**  **Mild\*** | **Group C**  **Moderate** | **Group D**  **Severe** | **Group E**  **Renal**  **Dialysis** |
| **BSA-indexed eGFR\*\*** | ≥80\*\*\* | 50-79\*\*\* | 30-49\*\*\* | <30 | Any |

\* The Mild group will not enroll patients, unless tolerability or pharmacokinetic differences are observed between Normal and Moderate cohorts.

\*\* The (BSA-indexed) eGFR is determined using the procedure described in Section 6.2.

\*\*\* Based on the 1998 FDA Guidance for Industry “Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling”

**INVESTIGATIONAL AGENT**

*Please state route and schedule of Study Agent administration, and enter exact doses for each dose level and group in the table below. (For example, “Agent XXX is given intravenously as a 1-hour infusion on days 1, 3, and 5 of a 21-day cycle.”)*

*[CTEP IND Agent]* is given *[route, duration]* on *[day(s)]* of a *[#-day]* cycle.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Group A** | **Group B** | **Group C** | **Group D** | **Group E** |
| **Dose**  **Level** | **Normal renal function**  **(** (*units)* **)\*** | **Mild renal dysfunction**  **(** (*units)* **)\*** | **Moderate renal dysfunction (** (*units)* **)\*** | **Severe renal dysfunction (** (*units)* **)\*** | **Renal**  **dialysis (** (*units)* **)\*** |
| **Level –1** |  | TBD\*\* |  |  | \*\*\* |
| **Level 1** |  | TBD\*\* |  |  | \*\*\* |
| **Level 2** |  | TBD\*\* |  |  | \*\*\* |
| **Level 3** |  | TBD\*\* |  |  | \*\*\* |
| **Level 4** |  | TBD\*\* |  |  | \*\*\* |
| *\** *Doses are stated as exact dose in clinically utilized units (e.g., mg/m2, mcg/kg, etc.) rather than as a percentage.*  *\*\** *To be determined based on the safety data available for Normal and Moderate at the time that this group potentially would be activated for enrollment*  \*\*\* (See Section 6.2 for the Group E dosing scheme.) | | | | | |

Note: **This schema is not to be used for determining dosage for any individual patient. For specific dosing information, please refer to Sections 6 and 7.**

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# OBJECTIVES

## Primary Objectives

* + 1. *[Hepatic only]* To establish the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of *[CTEP IND Agent]* in groups of patients with varying degrees of hepatic dysfunction (mild, moderate, and severe) in order to provide appropriate dosing recommendations for *[CTEP IND Agent]* in such patients.

*OR*

*[Renal only]* To establish the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of *[CTEP IND Agent]* in groups of patients with varying degrees of renal dysfunction (moderate, severe, and dialysis) in order to provide appropriate dosing recommendations for *[CTEP IND Agent]* in such patients.

* + 1. To characterize the pharmacokinetic (PK) and pharmacodynamic profiles of *[CTEP IND Agent]* in patients with varying degrees of *[hepatic/renal]* dysfunction.

## Secondary Objectives

* + 1. To document the non-DLTs associated with administration of *[CTEP IND Agent]* in patients with *[hepatic/renal]* dysfunction.
    2. *[Hepatic only]* To correlate novel markers/scores of hepatic dysfunctions with the observed toxicities, plasma PK, and PD of *[CTEP IND Agent]* administration; these may include MELD, Maddrey, the Mayo Survival Model for Primary Biliary Cirrhosis, or the Revised Natural History Model for Primary Sclerosing Cholangitis.
    3. *[Renal only]* To measure GFR with an external marker of filtration (*e.g.* iohexol). This approach represents the standard for determining kidney function and allows future comparison of measured GFR with various estimators of GFR and pharmacokinetics.
    4. *[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.
    5. *[Renal only]* To bank a pretreatment serum sample obtained from patients at the EET Biobank at Nationwide Children's Hospital for future generation of estimators of renal function.

# BACKGROUND

## Study Disease(s)

*For phase 1 or 2 disease-specific studies, please provide background information on the study disease.*

## CTEP IND Agent

*Please provide background information below on the CTEP IND study agent, including 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 hepatic, renal, metabolic, or drug interactions, if any (*e.g.*, via the P450 enzyme system).*

## Rationale for a Phase 1 Study in Patients with *[Hepatic/Renal]* Dysfunction

*[Hepatic] Please provide the background and rationale for evaluating this agent in patients with hepatic dysfunction including information such as the primary mode of excretion of the agent, its therapeutic index, and why this particular patient population has been chosen for study. FDA guidance on PK studies in patients with hepatic dysfunction can be found at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>.

*[Renal] Please provide the background and rationale for evaluating the study agent in patients with renal dysfunction including information such as the primary mode of excretion of the agent, its therapeutic index, and why this particular patient population has been chosen for study. Guidance on PK studies in such patients can be found at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072127.pdf>.

## *[Hepatic]* Classification by Liver Dysfunction *OR [Renal]* Stratification by Level of Renal Dysfunction

*[Hepatic]* The Child-Pugh Classification (CPC) of liver dysfunction was first proposed by Child and Turcotte in 1964 as a means of estimating hepatic functional reserve in candidates for porto-caval shunt surgery (Child and Turcotte, 1964; Turcotte and Lambert, 1973), and has more recently been used to assess prognosis in a variety of chronic liver diseases (Conn *et al*., 1981; Conn, 1981; Shetty *et al*., 1997). While the CPC is often used alone or with other variables for staging patients with hepatocellular carcinoma (Levy *et al*., 2002; Parasole *et al*., 2001), the method has not been validated for the assessment of liver function in patients with other neoplasms. In addition, it is not clear whether the CPC correlates with elimination of drugs metabolized by the liver (Grasela *et al*., 2000; Khaliq *et al*., 2000; Schaad *et al*., 1997). For these reasons, total bilirubin and SGOT/AST levels will be used as a measure of hepatic dysfunction for the study. These values are readily available for cancer patients and at present, are commonly used to evaluate their hepatic function. Information on the CPC status of patients in this study will be collected in a prospective manner and an attempt will be made to correlate these data with the observed toxicities and PK and pharmacodynamics of *[CTEP IND Agent]*. A copy of the CPC is provided in Appendix A.

The MELD was originally developed to predict the mortality of patients who underwent a transjugular intrahepatic portosystemic shunt procedure and has since found other applications for patients with liver dysfunction (Kamath PS, et al. 2007). In particular, it is used to prioritize patients for liver transplants. The MELD is calculated using creatinine, bilirubin and the international normalized ratio for prothrombin time (INR). The formula to calculate MELD is provided in Appendix A.

The Maddrey discriminant function (df) was developed to evaluate the potential efficacy of corticosteroid used to treat alcoholic hepatitis. The Maddrey df is calculated using prothrombin time and bilirubin. The formula to calculate Maddrey df is provided in Appendix A.

The Mayo Survival Model for Primary Biliary Cirrhosis (Dickson *et al*., 1989) and the Revised Natural History Model for Primary Sclerosing Cholangitis (Kim *et al*., 2000) were designed to calculate the survival probability and thus treatment options for the respective conditions. The Mayo Survival Model for Primary Biliary Cirrhosis is calculated using age, albumin, bilirubin, edema, prothrombin time. The Revised Natural History Model for Primary Sclerosing Cholangitis is calculated using age, albumin, bilirubin, aspartate aminotransferase, and variceal bleeding. The formula to calculate the Mayo models are provided in Appendix A.

*[Renal]* Renal function levels in clinical trials have commonly been described in terms of creatinine clearance (CrCl) calculated using a formula such as Cockcroft-Gault (Cockcroft and Gault, 1976). This formula estimates CrCl based on the serum creatinine concentration in addition to demographic data. However, MDRD, and more recently CKD-EPI have proven to be more accurate and precise estimators of GFR. In addition, they result in estimates that are already normalized to BSA, thereby providing a renal function estimate that is physiologically informative, and does not penalize small people. (See Section 6.2 for details of this procedure.)

While the glomerular filtration rate (GFR) is generally accepted as a superior overall measure of renal function compared to CrCl, the best methods for GFR determination (inulin clearance, 125I-iothalamate, etc.) are not readily available or are impractical in the patient care setting.

**This trial will use BSA-normalized eGFR to stratify patients rather than renal dysfunction measurements based on the Cockcroft-Gault formula or GFR.**

## 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” (*[*https://ctep.cancer.gov/protocolDevelopment/templates\_applications.htm*](https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm)*). If this trial includes no correlative studies, this section should be marked “N/A”.*

# PATIENT SELECTION

## Eligibility Criteria

*Note for all protocols: If the study has an integral biomarker to determine eligibility to study or specific treatment arms, then the relevant eligibility criteria must be stated (*e.g.*, Presence of [specific gene mutations and variants]). Integral biomarker information must also be included in and be consistent with the Biomarker Plan Table and Section 5.*

* + 1. *Please select the appropriate text below and delete the unused text. Patients with hematologic malignancies should not be included in the study of an agent where myelosuppression is known to be dose limiting.*

Patients must have histologically or cytologically confirmed solid or hematologic malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

*[Hepatic]* Patients with a liver mass, raised α-fetoprotein level (≥500 ng/mL) and positive serology for hepatitis, consistent with a diagnosis of hepatocellular carcinoma will be eligible without the need for pathologic confirmation of the diagnosis.

*OR*

Patients must have histologically or cytologically confirmed solid malignancy or lymphoma that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

*[Hepatic]* Patients with a liver mass, raised α-fetoprotein level (≥500 ng/mL) and positive serology for hepatitis, consistent with a diagnosis of hepatocellular carcinoma will be eligible without the need for pathologic confirmation of the diagnosis.

*OR*

Patients must have histologically or cytologically confirmed advanced hematologic malignancy for which standard curative or palliative measures do not exist or are no longer effective.

* + 1. Age ≥18 years.
    2. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix C).
    3. *[Please use the following criteria for hepatic dysfunction trials, and delete the other set of criteria below.]* Patients must have adequate organ and marrow function as defined below:
* absolute neutrophil count ≥1,000/mcL
* platelets ≥100,000/mcL
* glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2.

*OR*

*[Please use the following criteria for renal dysfunction trials, and delete the other set of criteria above.]* Patients must have adequate organ and marrow function as defined below:

* absolute neutrophil count ≥1,000/mcL
* platelets ≥100,000/mcL
* total bilirubin within normal institutional limits
* AST(SGOT)/ALT(SGPT) ≤3 × institutional upper limit of normal

1. *Laboratory test results should only be used as exclusion criteria when scientifically justified and when abnormal test results confer safety concerns.*
2. *Laboratory reference values should account for potential normal variations due to race, ethnicity, age, sex, and gender identity (*e.g.*, due to surgical and/or hormonal changes).*

* + 1. *[Hepatic]* Patients with normal or abnormal liver function will be eligible and will be grouped according to the criteria in Section 6.1. Patients with active hemolysis should be excluded. No distinction will be made between liver dysfunction due to metastases and liver dysfunction due to other causes. If the specific cause of hepatic dysfunction is unknown, the patient should be worked up for other viral causes of hepatitis and their eligibility determined after consultation with the Principal Investigator. Liver function tests should be repeated within 24 hours prior to starting initial therapy.

*OR*

*[Renal]* Patients with normal or abnormal renal function will be eligible and will be grouped according to the criteria in Section 6.2. Kidney function tests should be repeated within 24 hours prior to starting initial therapy.

* + 1. *[Hepatic]* Patients with biliary obstruction for which a shunt has been placed are eligible, provided the shunt has been in place for at least 10 days prior to the first dose of *[CTEP IND Agent]* and the liver function has stabilized. Two measurements at least 2 days apart that put the patient in the same hepatic dysfunction stratum will be accepted as evidence of stable hepatic function. There should be no evidence of biliary sepsis.
    2. *Do not mandate minimum washout periods from previous treatment unless scientifically justified and clearly specified. In deciding whether time-based washout periods are appropriate, investigators should consider whether recent prior therapy will affect toxicity, drug-drug interaction or misattribution of effect. In all cases, rationale for the washout period should be specified in the protocol:*
* *For agents/regimens later in development, longer washout periods are probably inappropriate since toxicity is better defined.*
* *Washout requirements should be restricted to specific agents or classes of agents with overlapping toxicity or potential drug-drug interaction.*
* *If there is strong evidence that a prior exposure to an agent or regimen may have delayed response, or ongoing influence on* *progression-free survival (PFS), a longer washout period may be appropriate.*
  + 1. *Prior therapy: Patients should be eligible for clinical trials regardless of the number or type of prior therapies and without a requirement to have received a specific therapy prior to enrollment unless a scientific or clinically based rationale is provided as justification.*

*Define as appropriate any limitations on prior therapy providing a scientific or clinically based rationale for justification (*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 site/total dose for prior radiation exposure as needed (*e.g.*, no more than 3000 cGy to fields including substantial marrow involvement).*

* + 1. 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 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. *[****If appropriate for agent and trial design:****]* 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. *Please use or modify the following paragraph as appropriate.*

The effects of *[CTEP IND Agent]* on the developing human fetus are unknown. For this reason and because *[Agent Class]* agents are known to be teratogenic, 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 *[CTEP and/or CIP IND Agent]* administration.

* + 1. Ability to understand and the willingness to sign a written informed consent document. Legally authorized representatives may sign and give informed consent on behalf of study participants.

## Exclusion Criteria

*Note for all protocols: If the study has an integral biomarker to determine exclusion from study or specific treatment arms, then the relevant exclusion criteria must be stated (*e.g.*, Presence of [specific gene mutations and variants]). Integral biomarker information must also be included in and consistent with the Biomarker Plan Table and Section 5.*

* + 1. *[Use the following text for hepatic dysfunction studies.]* Patients who have been treated with agents that persist in the body for longer than 4 to 6 weeks (such as suramin) are ineligible during the elimination period for those agents.
    2. *If washout period(s) and/or degree of prior therapy is(are) not addressed in the Eligibility Criteria, it(they) may be included here. Please see sections 3.1.3 and 3.1.4. (This information should not be included in both inclusion and exclusion criteria.)*
    3. 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. *[if appropriate]*
    4. Patients who are receiving any other investigational agents.
    5. *The investigator(s) must state a medical or scientific reason if patients who have brain metastases will be excluded from the study. (This information should not be included in both inclusion and exclusion criteria.)*
    6. History of allergic reactions attributed to compounds of similar chemical or biologic composition to *[CTEP IND Agent]*.
    7. *Concomitant medications: Patients should only be excluded from trial participation when clinically relevant known or predicted drug-drug interactions or potential overlapping toxicities will impact safety or efficacy. Please include scientific or clinically based rationale for exclusion.*

*Please note that this must account for all agents to be used on this study, including commercial agents. Please refer to the FDA product labels for all commercial agents and include information on prohibited concomitant medications in all applicable sections of the protocol (see also Section 6.7). [Appendix F is a sample patient information sheet that can be tailored to this specific protocol and presented to the patient*.*]*

* + 1. Patients with uncontrolled intercurrent illness or any other significant condition(s) that would make participation in this protocol unreasonably hazardous.
    2. *The investigator(s) must state a medical or scientific reason if pregnant or nursing patients will be excluded from the study. The full text of the Policies, Guidelines, and Procedures pertinent to this requirement is available on the CTEP website (*[*http://ctep.cancer.gov/protocolDevelopment/policies\_pregnant.htm*](http://ctep.cancer.gov/protocolDevelopment/policies_pregnant.htm)*). Suggested text is provided below:*

Pregnant women are excluded from this study because *[CTEP IND Agent]* is *[a/an Agent Class]* agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with *[CTEP IND Agent],* breastfeeding should be discontinued if the mother is treated with *[CTEP IND Agent]*.

* + 1. *The investigator(s) must state a medical or scientific reason if patients who are cancer survivors will be excluded from the study. The full text of the Policies, Guidelines, and Procedures pertinent to this requirement is available on the CTEP website (*[*http://ctep.cancer.gov/protocolDevelopment/policies\_hiv.htm*](http://ctep.cancer.gov/protocolDevelopment/policies_hiv.htm)*).*
    2. *Please insert other appropriate agent-specific exclusion criteria.*

## Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see <http://grants.nih.gov/grants/funding/phs398/phs398.pdf>.

*Describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study and complete the format in the Planned Enrollment Report (table provided under Section 9.2).*

# REGISTRATION PROCEDURES

## Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at <https://ctepcore.nci.nih.gov/rcr/>. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to ETCTN trials.

* Investigator (IVR): MD, DO, or international equivalent,
* Non Physician Investigator (NPIVR): advanced practice providers (*e*.*g*., NP or PA) or graduate level researchers (*e*.*g*., PhD),
* Associate Plus (AP): clinical site staff (*e*.*g*., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges, and
* Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

| **Documentation Required** | **IVR** | **NPIVR** | **AP** | **A** |
| --- | --- | --- | --- | --- |
| CTEP-IAM Account with ID.me credentials | ✔ | ✔ | ✔ | ✔ |
| FDA Form 1572   * Practice sites, IRBs, and labs | ✔ | ✔ |  |  |
| Financial Disclosure Form | ✔ | ✔ | ✔ |  |
| NCI Biosketch (education, training, employment, certification, licensure, ABMS certification, GCP Training, personal statement, memberships, honors, publications, research support) | ✔ | ✔ | ✔ |  |
| GCP Training Certificated (mandatory file upload) | ✔ | ✔ | ✔ |  |
| Agent Shipment Form (if applicable) | ✔ |  |  |  |
| CV (optional file upload) | ✔ | ✔ | ✔ |  |
| Annual Re-registration | ✔ | ✔ | ✔ | ✔ |

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

* Addition to a site roster,
* Selection as the treating, credit, or consenting person in OPEN,
* Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
* Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the [NCI RCR](https://ctep.cancer.gov/investigatorResources/default.htm) page on the [CTEP website](https://ctep.cancer.gov) for additional information. For questions, please contact the **RCRHelp Desk** by email at [RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov).

## Site Registration

|  |
| --- |
| *This section applies to*  ***ETCTN and other CTMS-monitored***  *trials (CTMS-Routine and CTMS-Comprehensive). Non-Network/non-CTMS trials may delete all text under 4.2 and replace with “N/A”.* |

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

**IRB Approval**

*If this is an ETCTN trial, remove the first paragraph below:*

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB prior to March 1, 2019. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating through the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB’s approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [CTSURegPref@ctsu.coccg.org](mailto:CTSURegPref@ctsu.coccg.org) to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email ([CTSURegPref@ctsu.coccg.org](mailto:CTSURegPref@ctsu.coccg.org)) or by calling 1-888-651-CTSU (2878).

*For trials that will include sites using their local IRB or REB as well as for a trial with non-U.S.-based NCTN and NCORP sites, include the following paragraph and the three associated bullet points:*

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

* Local IRB documentation,
* IRB-signed CTSU IRB Certification Form, and/or
* Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol PI (*i*.*e*., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

* Have an active CTEP status,
* Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization’s roster,
* If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
* Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
* List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
* Have the appropriate CTEP registration type for the protocol.

**Additional Requirements**

Additional site requirements to obtain an approved site registration status include:

* An active Federal Wide Assurance (FWA) number,
* An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
* An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
* Compliance with all applicable protocol-specific requirements (PSRs).
  + 1. Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members’ website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

* Log in to the CTSU members’ website ([https://www.ctsu.org](https://www.ctsu.org/))
* Click on *Protocols* in the upper left of the screen
  + Enter the protocol number in the search field at the top of the protocol tree, or
  + Click on the By Lead Organization folder to expand, then select *[Corresponding Organization]*, and protocol number *[NCI Protocol #]*,
* Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)
  + 1. Protocol Specific Requirements For *[NCI protocol #]* Site Registration
* *If applicable, add any other protocol-specific documents or requirements (e.g., site or investigator specialized credentialing, evidence of training, study-specific regulatory forms) needed for site registration. Include any processing instructions, or reference the location in the protocol or appendices where further instructions can be found.*
  + - *[If this study uses the ETCTN Specimen Tracking System, also include:]* Specimen Tracking System Training Requirement:
    - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time.
    - This training will need to be completed before the first patient enrollment at a given site.
    - Please contact STS Support at Theradex for the training ([STS.Support@theradex.com](mailto:STS.Support@theradex.com)).
    1. Submitting Regulatory Documents

*Add additional protocol-specific details in this section as needed.*

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members’ website.

To access the Regulatory Submission Portal, log on to the CTSU members’ website, go to the *Regulatory* section, and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or [CTSURegHelp@coccg.org](mailto:CTSURegHelp@coccg.org) to receive further instruction and support.

*For studies with a Delegation of Tasks Log [DTL], add the following section on DTL. Note that all ETCTN studies require the use of a DTL.*

**Delegation of Tasks Log (DTL)**

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members’ website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describes DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

*If the DTL has training requirements or task assignment restrictions, include the following two sections.*

The DTL for this study has training requirements as follows:

*{Add description of training requirement for this study and the task it is linked to}*

In addition, the following task assignment restrictions apply to this protocol:

*{Add description of task assignment restrictions (e.g., persons assigned the Unblinded Study Personnel task may not be assigned other tasks except Investigational Agent Accountability. There must be at least two persons assigned to the Unblinded Study Personnel task.)}*

The individual initiating the DTL for the site should upload the above listed training documentation when making the task assignment. The designated reviewer will accept or reject the documentation. A note regarding rejection of any training documents will display on the Site DTL Browser next to the task assignment. The DTL cannot be submitted for CI sign-off until the minimum number of persons are assigned to the task and have met the training requirements.

* + 1. Checking Site Registration Status

Site’s registration status may be verified on the CTSU members’ website.

* Click on *Regulatory* at the top of the screen,
* Click on *Site Registration*, and
* Enter the site’s 5-character CTEP Institution Code and click on Go.
  + Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator’s status with NCI or their affiliated networks.

## Patient Registration

* + 1. OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI’s clinical data management system, Medidata Rave.

Requirements for OPEN access:

* Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
* To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
* If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
* Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Boards (IRB) number used on the site’s IRB approval on their Form Food and Drug Administration (FDA) 1572 in Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

* Patient has met all eligibility criteria within the protocol stated timeframes, and
* All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note:  The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at <https://open.ctsu.org> or from the OPEN link on the CTSU members’ website. Further instructional information is in the OPEN section of the CTSU website at <https://www.ctsu.org> or <https://open.ctsu.org>. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

*If using slot reservations, keep the following paragraph and edit the two bullet points as needed:*

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

* *If specific person-level attributes (e.g., neurocognitive certification, surgical credentialing) are required for site staff before enrollment, add to this section.*
* *For non-ETCTN trials and/or if applicable, add language to describe site reimbursements for specific tests and/or bio-specimen submissions that may trigger additional funding.* 
  + *For example, site submission of optional or conditional blood draws: To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Refer to the protocol-specific funding page on the CTSU members’ website for additional information (Protocol xxx >Funding Information). Timely entry of completion dates is recommended as this will trigger site reimbursement.*
    1. Special Instructions for Patient Enrollment

*Include any special instructions related to slot reservations or patient enrollment. For example, if sites must reserve a slot in IWRS and then submit documentation to the study team before their slot request will be approved and they are able to enroll the patient in OPEN, describe that here, including a listing of all required documents/steps. Otherwise this sub-section can be deleted.*

*If this study uses the ETCTN Specimen Tracking System, also include the following text:*

This Study will use the ETCTN Specimen Tracking System (STS).

* All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
* The system is accessed through Rave user roles: “Rave CRA” and “Rave CRA (Labadmin)” for data entry at the treating institutions and “Biorepository” for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
* Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
* **Important:** **Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section 5.4.

* + 1. OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

*Keep the following paragraph if using slot reservation; otherwise, it can be removed (one paragraph):*

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: <http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11>. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; [CTMSSupport@theradex.com](mailto:CTMSSupport@theradex.com).

## General Guidelines

Following registration, patients should begin protocol treatment within *[# of days]* days.\* Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient’s registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

*[\*Note: For leukemia protocols, treatment should be started as rapidly as possible.]*

# BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

*If this trial does not include correlative or special studies, this section should be marked “N/A” and all instructions as well as the text below deleted.*

## Summary Table for Specimen Collection

*Update the table below with protocol-specific time points, specimen types and amounts, and laboratory(-ies) to which sites should submit specimens. For each specimen, indicate whether specimen collection is mandatory or optional. All information in the tables in Section 5, along with the study calendar in Section 11, need to be consistent in the timing of specimen collection.*

*When specimens collected to determine eligibility are submitted to the EET Biobank or a central (non-local) laboratory for testing, then specimens must be labeled with identifiers from the STS. In those instances, the protocol will utilize multi-step registration and the statement below must be included.  This would be indicated by inclusion of a pre-enrollment timepoint in the Specimen Collection Table.  This paragraph should not be included when specimens are collected at pre-enrollment for “local testing” as these specimens will not be tracked in the STS.*

This protocol utilizes a multi-step registration. Patients must be enrolled on the first step of the registration prior to specimen collection and submission, so that specimens for eligibility can be tracked in the RAVE Specimen Tracking System and specimen identifiers can be assigned. Specimens not entered in the RAVE STS and assigned identifiers will not be processed.

|  |  |  |
| --- | --- | --- |
| **Time Point** | **Specimen** | **Send Specimens To:** |
| **Archival** | | |
|  | * *Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)1 (mandatory)*   *If a block is not available, then submit:*   * *1 H&E stained slide (3-5 µm)* * *30-50 unstained, uncharged, air-dried slides (10 µm). If not feasible, then a minimum of 20 unstained air-dried uncharged slides (10 µm) should be submitted with a minimum tumor content of 30-40%2.* | *EET Biobank* |
| **Baseline** | | |
|  | * *2 tumor cores in formalin3 (mandatory)* * *10 mL blood in Streck cfDNA tube (mandatory)* | *EET Biobank* |
| * *[Specimen type]* | *[Lab Name]* |
| ***[Time point #3]*** | | |
|  | * *2 tumor cores in formalin3 (optional)* * *10 mL blood in Streck cfDNA tube (mandatory)* | *EET Biobank* |
| * *[Specimen type]* | *[Lab Name]* |
| ***[Time point #4]*** | | |
|  | * *2 tumor cores in formalin3 (optional)* * *10 mL blood in Streck cfDNA tube (mandatory)* | *EET Biobank* |
| * *[Specimen type]* | *[Lab Name]* |
| **Progression** | | |
|  | * *2 tumor cores in formalin3 (mandatory)* * *10 mL blood in Streck cfDNA tube (optional)* | *EET Biobank* |
| * *[Specimen type]* | *[Lab Name]* |
| 1*[Use for archival specimens (blocks or slides) being sent to EET Biobank]* For archival tissue, **a copy of the anatomic pathology report corresponding to the tissue collection procedure must be sent with the tissue and uploaded to Rave**. If submitting slides, then slides must be processed in order, and numbered sequentially (*e.g*., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51 *[edit total slide # to match the total # of slides being sent to the EET Biobank*]).  2*[Include for archival slides being sent to the EET Biobank for NGS testing (WES/RNAseq/Oncomine) through the NCLN]* ***Submission of specimens with <30% tumor content may not provide sufficient material for analysis.***  3*[Use the following language for new research-only biopsy specimens being sent to the EET Biobank]* For new biopsies, **the Tissue Biopsy Verification Form (Appendix *G)*, a copy of the radiology and/or operative reports from the tissue collection procedure *and* the diagnostic anatomic pathology report** (i.e., the most recent anatomic pathology report specifying the diagnosis) must be sent with the tissue to the EET Biobank.  *[****OR*** *Use the following language for new surgical tissue being sent to the EET Biobank in formalin, frozen, or fresh]* For surgical tissue, submitted fresh, frozen, or in formalin, **the Tissue Biopsy Verification Form (Appendix *G)*, a copy of the radiology and/or operative reports from the tissue collection procedure *and* the diagnostic anatomic pathology report** (i.e., most recent anatomic pathology report specifying the diagnosis) must be sent with the tissue to the EET Biobank.  If the Corresponding Pathology Report from the surgery becomes available after shipment of specimens to the EET Biobank, then it must be sent to the EET Biobank via secure email and uploaded to Rave.  *[****OR*** *Use the following language for new FFPE surgical specimens being sent to the EET Biobank]* For FFPE surgical tissue, **upload the Corresponding Pathology Report from the surgery to Rave and send a copy to the EET Biobank** with the tissue**.**  Please hold submission of the FFPE surgical tissue to the EET Biobank until the Corresponding Pathology Report is available.  *[****OR*** *Use the following language if bone marrow aspirate or a bone marrow core biopsy is collected]* **For bone marrow aspirate or biopsy, the bone marrow report corresponding to the bone marrow collection procedure must be uploaded to Rave and sent with the specimen to the EET Biobank.** | | |

## Summary Table(s) for Interventional Radiologist for Research Biopsies

*An Interventional Radiologist (IR; defined as those Radiologists responsible for the acquisition of biopsy specimens) should be consulted during the preparation of the protocol involving any core biopsy procedures and to assure that a system is in place for patient assessment and consultation prior to undergoing a procedure to obtain tissue specimens.*

*Complete the following table for each biopsy procedure indicated in the Summary Table for Specimen Collection (Section 5.1). Duplicate the table as needed.*

*For* ***IR Biopsy Definition****, each biopsy should be categorized as either:*

* ***Research – Clinical Impact*** *as defined in IR SOP (*[https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN\_IR\_Research\_Biopsy\_SOP.pdf](https://na01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fctep.cancer.gov%2FinitiativesPrograms%2Fdocs%2FETCTN_IR_Research_Biopsy_SOP.pdf&data=01%7C01%7Cjsager%40tech-res.com%7Cf468cc828dcf4b51979c08d698d7e103%7C806430642666421e89e796efca3d7489%7C0&sdata=Fbt0UmITgBEKLuX%2Fkcvndg0XjGz42xvk1w5L53FPuXw%3D&reserved=0)*): One or more cores from a single biopsy procedure will be used for integral biomarker(s), used to directly impact patient care.*

*OR*

* ***Research – No Clinical Impact*** *as defined in IR SOP (*[https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN\_IR\_Research\_Biopsy\_SOP.pdf](https://na01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fctep.cancer.gov%2FinitiativesPrograms%2Fdocs%2FETCTN_IR_Research_Biopsy_SOP.pdf&data=01%7C01%7Cjsager%40tech-res.com%7Cf468cc828dcf4b51979c08d698d7e103%7C806430642666421e89e796efca3d7489%7C0&sdata=Fbt0UmITgBEKLuX%2Fkcvndg0XjGz42xvk1w5L53FPuXw%3D&reserved=0)*): All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.*

*For each biopsy core in order of priority, provide the* ***use in the trial*** *(*i.e.*, integral, integrated, or exploratory) and* ***biomarker name*** *(*e.g.*, specific gene mutations, proteins, cells,* etc.*) of the biomarker that will use the core, and* ***post-biopsy processing*** *(*e.g.*, formalin or frozen).* ***The total number of cores listed for a given time point should be equal to the number of cores collected at that time point as defined in Section 5.1. The biopsy post-processing should also be consistent with Section 5.1. If a biomarker will utilize more than one core, then those cores can be listed in a single row (e.g., 1&2). Additionally, if a core will be utilized for more than one biomarker assay, then all applicable biomarkers can be listed in the row for that core in order of priority. If there are different uses for these biomarkers, then all applicable uses should be listed in the row for that core (e.g., Integrated/Exploratory).***

***Note:***

*Cores 1 & 2 are obtainable in most circumstances and settings based on risk assessment (for lesions with pre-biopsy scores of 2-3).*

*Cores 3 & 4 are obtainable in some circumstances based on safety and risk assessment (for lesions with pre-biopsy scores of 2-3).*

*Cores 5 & 6 are RARELY obtainable based on safety and risk assessment, including lesion size and location.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Biopsy #:** *[Add biopsy number,* e.g.*, 1, 2, 3,* etc.*]* | | | |
| **Trial Time Point:** *[Add trial time point,* e.g.*, Baseline]* | | | |
| **IR Biopsy Definition:** *[Add either “Research – Clinical Impact (One or more cores from a single biopsy procedure will be used for integral biomarker(s), used to directly impact patient care.)” OR “Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.)”]* | | | |
| **Core Priority** | **Use in the Trial** | **Biomarker Name(s)** | **Post-Biopsy Processing** |
| 1 | *[Add use(s), e.g., Integral, Integrated, or Exploratory]* | *[Add biomarker name(s)]* | *[Add post-biopsy processing,* e*.*g*., formalin, frozen, or FFPE, etc.]* |
| 2 | *[Add use(s), e.g., Integral, Integrated, or Exploratory]* | *[Add biomarker name(s)]* | *[Add post-biopsy processing,* e*.*g*., formalin, frozen, or FFPE, etc.]* |
| 3 | *[Add use(s), e.g., Integral, Integrated, or Exploratory]* | *[Add biomarker name(s)]* | *[Add post-biopsy processing,* e*.*g*., formalin, frozen, or FFPE, etc.]* |
| 4 | *[Add use(s), e.g., Integral, Integrated, or Exploratory]* | *[Add biomarker name(s)]* | *[Add post-biopsy processing,* e*.*g*., formalin, frozen, or FFPE, etc.]* |
| 5 | *[Add use(s), e.g., Integral, Integrated, or Exploratory]* | *[Add biomarker name(s)]* | *[Add post-biopsy processing,* e*.*g*., formalin, frozen, or FFPE, etc.]* |
| 6 | *[Add use(s), e.g., Integral, Integrated, or Exploratory]* | *[Add biomarker name(s)]* | *[Add post-biopsy processing,* e*.*g*., formalin, frozen, or FFPE, etc.]* |

*Add/delete rows as needed for planned number of biopsy cores.*

**Note:** Pre-biopsy assessments will be reported and tracked through a trial-specific Case Report Form (CRF) within the CTEP Medidata Rave system (see Appendix E).

## Specimen Procurement Kits and Scheduling

* + 1. Specimen Procurement Kits

*Provide instructions about how sites can obtain specimen procurement kits. If procurement kits will not be provided, indicate that institutional supplies should be used for shipping specimens or mark this section “N/A”.*

*For specimens being shipped to the EET Biobank, include the following language about ordering kits through the Kit Management system:*

Kits for the collection and shipment of select specimens to the EET Biobank can be ordered online via the Kit Management system: (<https://kits.bpc-apps.nchri.org>).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kits per kit type per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

**Note:** Kits or supplies are only provided for specimens shipped to the EET Biobank. Institutional supplies must be used for all other specimen collection and processing.

* + 1. Scheduling of Specimen Collections

*Provide instructions about how sites should schedule specimen collections (*e.g.*, if tumor tissue in formalin must be shipped on the same day of collection, but can only be received at the biobank Tuesday through Thursday to allow time for processing, sites should be instructed to collect tumor tissue Monday through Wednesday) Remove any bullet points that are not applicable to your study Detailed instructions about specimen collection and shipping should be provided in Sections 5.5, 5.6, and 5.7, not here.*

*For specimens being shipped to the EET Biobank, the following standard language is provided for tumor tissue in formalin, frozen specimens, fresh blood or bone marrow and ambient specimens such as saliva or buccal cells. Please revise this list to only include specimen types that are applicable to your study:*

Please adhere to the following guidelines when scheduling procedures to collect tissue:

* Tumor tissue specimens collected during biopsy procedures and fixed in formalin must be shipped on the same day of collection.
* Tissue in formalin can be collected Monday through Wednesday and shipped overnight for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children’s Hospital.
* Tissue submitted as FFPE (blocks or slides) can be collected on any day but must be shipped to the EET Biobank on Monday through Thursday.
* Specimens submitted frozen *[list applicable specimens, such as frozen tissue, frozen stool, plasma, or serum]* can be collected on any day but must be stored frozen and shipped to the EET Biobank on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained in a -70°C to -80°C freezer.
* Fresh blood *[when applicable, also add: bone marrow, saliva, buccal cells, urine, etc. Use room temperature or ambient instead of fresh when specimens other than blood or bone marrow are collected.]* specimens may be collected and shipped Monday through Friday.

## Specimen Tracking System Instructions

|  |
| --- |
| *This section applies to* ***ETCTN*** *trials and other studies using the Specimen Tracking System (STS). Non-Network trials may modify the specimen tracking and labeling information as needed in this section or delete all text under 5.4 and replace with “N/A”.* |

* + 1. Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

* Protocol Number
  + - Investigator Identification
  + Institution and affiliate name
  + Investigator’s name
* Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
* Additional Requirements:
* Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies without a corresponding pathology report, the radiology and operative report(s) must also be uploaded into Rave, when available. **Important: Remove any personally identifying information, including, but not limited to, the patient’s name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at [STS.Support@theradex.com](mailto:STS.Support@theradex.com).

The Shipping List report **must** be included with all sample submissions.

* + 1. Specimen Labeling
       1. Blood [Bone Marrow, Saliva, Stool, or other non-tissue] Specimen Labels [remove this section if no liquid/non-tissue specimens will be collected]

Include the following on blood [*add “and bone marrow, saliva, etc.” as appropriate for protocol]* specimens (including whole blood and frozen, processed blood products – like serum and plasma [*update to include specimen types appropriate for protocol]*):

* Patient Study ID
* Universal Patient ID (UPID)
* Specimen ID (automatically generated by Rave)
* Time point
* Specimen type (*e.g.*, blood, serum)
* Laterality, if applicable *[bone marrow only]* (to be added by hand)
* Collection date *[If the study also requires recording the collection time on the label, include the time. If time is only required for a subset of specimens (e.g., only blood for PK), please indicate that]* (to be added by hand)
  + - 1. Tissue Specimen Labels [remove this section if no tissue specimens will be collected]

Include the following on all tissue specimens (*e.g.*, FFPE block, slides, or frozen tissue) or containers (*e.g.*, formalin jar):

* Patient Study ID
* Universal Patient ID (UPID)
* Specimen ID (automatically generated by Rave)
* Time point
* Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
* Tissue type (P for primary, M for metastatic or N for normal)
* Surgical pathology ID (SPID) number (when applicable)
* Block number from the corresponding pathology report (FFPE tissue, when applicable) *[if the study includes submission of FFPE tissue]*
* Collection date *[If the study also requires recording the collection time on the label, include the time. If time is only required for a subset of specimens, please indicate that]* (to be added by hand)
* Slide section number (only if archival tissue is submitted as slides) (to be added by hand) *[if study includes the submission of slides]*
  + - 1. Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5” high and 1.28” wide.

Text

Description automatically generated

The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: <https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/>

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e*.*g*., for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

**Space is provided at the bottom of the label for the handwritten date and optional time.** The last line on the example label is for the handwritten date and optional time.

* + 1. Overview of Process at Treating Site
       1. OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

*Select the appropriate registration instructions from the following two options (either “Registration without eligibility specimen analysis:” OR “Registration with eligibility specimen analysis:”).*

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Registration with eligibility specimen analysis *[use only if tissue is being collected on study for eligibility testing which requires tracking by the STS (i.e., there is a pre-enrollment time point in the Specimen Collection Table in Section 5.1 with specimens being sent to a location other than “local testing”*]:

1. Site enters first step data into OPEN.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends first step registration data, including the IDs and a TAC of “NOT REG” directly to Rave.
4. The specimen tracking system in Rave is utilized for the specimen that contributes to eligibility determination.
5. Site enters second and any subsequent step data into OPEN including results of specimen analysis.
6. IWRS receives all data from OPEN, then sends it onto Rave with either the treatment TAC or a TAC of “SCRN FAIL”.
7. In addition to the specimen tracking forms completed to determine eligibility, data entry for screen failure patients should include Histology and Disease, all forms in the Baseline folder, any lab forms connected to eligibility determination, and Off Treatment/Off Study.

Any data entry errors made during enrollment should be corrected in Rave.

* + - 1. Rave Specimen Tracking Process Steps

**Step 0**: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

**Step 1**: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

* **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

**Step 2**: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

* Label specimen containers and write collection date *[if the study also requires recording the collection time on the label, include the time]* on each label. After collection, store labeled specimensas described in Section 5.5.
* Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Bone Marrow [*if bone marrow is submitted]*, Molecular Reports (up to 4), and Surgical (or Operative) reports. Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or the Tissue Biopsy Verification form (when applicable). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted**. Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document** (either by adding a label or hand writing).

**Step 3**: Complete specimen data entry.

* **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

*[Include the following text if frozen tissue, mononuclear cell pellets from bone marrow, or PBMC cell pellets from blood are collected for use by the NCLN PD Laboratories]*

* + For [frozen tissues or mononuclear cell pellets from [bone marrow or blood] *(select the appropriate specimen type(s))*] collected for the NCLN PD Laboratories**, the following must be recorded.**
    - **Time of collection -** Record times using military time (24-h designation); for example, specify 16:15 to indicate 4:15 PM.
    - **If the tissue specimens were flash frozen within 2 minutes from collection or not – Y/N**. If N is entered, record the actual time elapsed from collection to frozen in the following field**. See screenshot from Rave below.** *(include this bullet only for frozen tissue)*****

**Step 4**: When ready to ship, enter shipment information.

* **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
* **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

**Step 5**: Print shipping list report and prepare to ship.

* Shipping List report is available at the site level.
* Print two copies of the shipping list, one to provide in the box, the other for your own records.
* Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

**Step 6**: Send email notification.

* For only one of the specimens in the shipment, click “Send Email Alert” checkbox on the **Shipping Status** CRFto email recipient.

**Step 7:** Ship the specimen(s).

**Step 8**: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

## Specimen Collection

*Provide explicit instructions for the collection and preservation of specimens prior to shipping. Instructions should be provided for each specimen being collected on this study.*

***For specimens being shipped to the EET Biobank for biobanking and/or analysis through NCLN laboratories or any other identified laboratories, example specimen collection and preservation procedures are provided below. For trials submitting frozen biopsies to the NCLN Pharmacodynamics Laboratory, please include Appendix H. Note: The language provided below is meant to provide a starting point for routine specimen collections. The translational PI should discuss any requirements for specimen collection with the individual laboratory PIs conducting the study and modify these sections as appropriate. Sections that are not relevant should be deleted.***

Proper tissue embedding and orientation are necessary in order to support the sample and prevent tissue damage or loss during sectioning (as well as preserve diagnostic histological features). Improperly embedded tissue (e.g., needle cores) can provide incomplete information if diagnostic material is not properly sectioned in a timely manner. Improper orientation of certain samples can prevent the evaluation of histological features that may affect survival or recurrence, like depth of tumor invasion and involvement of surgical margins of resection. In order to prevent tissue embedding and orientation errors, refer to the guidelines in Appendix (*Reference appendices I, J, K, and/or L as appropriate*. *Delete this paragraph if tissue is not collected or if tissue is shipped in formalin to the EET biobank. Delete any appendices that are not applicable for your study.)*

* + 1. Archival or Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously-collected FFPE tissue will be submitted, then the following criteria must be met:

* Tissue must have been collected within 6 months prior to registration
* FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
  + Surface area: 25 mm2 is optimal. Minimum is 5 mm2.
  + Volume: 1 mm3 optimal. Minimum volume is 0.2 mm3, however the success of DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available *(note: the text inserted below should be consistent with the Specimen Collection Table in Section 5.1 and the bullets listed in the same order)*:

* One (1) H&E slide (3-5 µm)
* Thirty to fifty (30 – 50) 10 µm unstained air-dried uncharged slides (preferred). If not feasible, then a minimum of twenty (20) 10 µm unstained air-dried uncharged slides should be submitted with a minimum tumor content of at least 30%. **Submission of specimens with <30% tumor content may not provide sufficient material for analysis** *[include for NGS-based biomarkers, if archival tissue is likely be to be* ***biopsies****; uncharged slides at 10-microns (µm) are preferred for slides intended for DNA/RNA extractions. Either the second or third bullet should be included, not both.]*
* Twenty (20) 10 µm unstained air-dried uncharged slides (preferred). If not feasible, then a minimum of ten (10) 10 µm unstained air-dried uncharged slides should be submitted with a minimum tumor content of at least 30%. **Submission of specimens with <30% tumor content may not provide sufficient material for analysis** *[include for NGS-based biomarkers, if archival tissue is likely to be to* ***resections****; uncharged slides at 10 microns (µm) are preferred for DNA/RNA extractions. Either the second or third bullet should be included, not both.]*
* *Add additional slides, including required thickness, charge, and baked/air-dried, if other analyses are planned that require archival tissue (e.g., IHC).*

Process and number slides sequentially (e.g., H&E stained slide should be created first and labeled with “1,” and additional unstained slides should be processed next and be labeled 2 – n) *[change “n” to match the number listed in the 5.1 Summary Table for Specimen Collection and footnote #1]*.

See Section 5.4.2 for labeling instructions.

* + 1. Formalin-Fixed Tumor Biopsies

1. Label formalin-filled containers according to instructions in Section 5.4.2.
2. Obtain [number] 16-gauge or 18-gauge core needle biopsy specimens, and place one core in each cassette.
3. Snap the cassette lids closed and place cassettes into a formalin-filled pre-labeled container as soon as possible after collection to prevent air drying. Up to two cassettes may be placed in one formalin jar.
4. Secure the container lids and package containers into the shipping kit according to instructions in Section 5.6. Keep tissue in formalin jars at room temperature until shipment to the EET Biobank.
   * 1. Collection of Snap-Frozen Biopsies *(Use these instructions when none of the frozen tissue specimens are collected for assays that will be performed by the NCLN PD Laboratories. Do not include Appendix H).*
5. Tissue should be frozen as soon as possible. Optimally, freeze within 30 minutes from resection.
6. Prior to tissue collection:
   1. Label cryovial(s) according to instructions in Section 5.4.2.
   2. Place cryovial(s) on dry ice to freeze. The vials should appear frosty when ready.
7. Immediately place tissue in foil and allow to completely freeze (using either direct contact with dry ice, or liquid nitrogen vapor).
8. Gently remove the frozen tissue from the foil. If the tissue is sticking to the foil, then gently run a finger over the back of the foil to loosen the tissue.
9. Using clean forceps place each tissue core in a separate pre-chilled cryovial. Tissue should move freely in the vial.
10. Place the tissue in a -70 to -80°C freezer. Keep frozen until shipment to the EET Biobank.
    * 1. Collection of Snap-Frozen Biopsies *(Use these instructions for* ***all*** *frozen tissue specimens in protocols where any frozen tissue specimens will be collected for assays that will be performed by the NCLN PD Laboratories and include Appendix H.)*
11. Follow the instructions in Section 5.3.1 to request specimen procurement kits for frozen sample collection before scheduled biopsy collection.
12. Biopsy specimens should be collected into pre-chilled 1.5mL Sarstedt, O-ring screw cap tubes (VWR, Cat#: 83009-010).
    1. Label Sarstedt tube(s) according to instructions in Section 5.4.2, prior to pre-chilling.
13. It is imperative that biopsies are flash frozen within **2 minutes** of collection in order to preserve key pharmacodynamic biomarkers.
14. As described in Appendix H, place the tissue in a pre-chilled cryovial and freeze the tube in liquid nitrogen or dry ice/ethanol bath.  Keep frozen in a -80 ºC or lower freezer until shipment to the EET Biobank.
15. **The following should be recorded and entered into the STS system in RAVE. This information is required to ensure proper analysis:**
    1. **Time of collection**. Record times using military time (24-h designation); for example, specify 16:15 to indicate 4:15 PM.
    2. **If the tissue specimens were flash frozen within 2 minutes from collection or not – Y/N.** If N is entered, record the actual time elapsed from collection to frozen in the following field.

Sites are **strongly encouraged** to contact the NCLN PD Laboratory at [NCI\_PD\_Support@mail.nih.gov](mailto:NCI_PD_Support@mail.nih.gov) to initiate training and clarify biopsy collection procedure.

* + 1. Collection of OCT-Embedded Frozen Biopsies *(Include these instructions when OCT-embedded tissue is collected. Include Appendix K. If OCT-embedded slides are collected, also include Appendix L.).*

1. OCT-embedded frozen biopsies must be labeled according to instructions in Section 5.4.2.
2. Please ensure tissue is oriented properly. Improperly oriented tissue is difficult to identify in opaque OCT and leads to complications when processing. See Appendices K and L for collection instructions.
3. Keep frozen at frozen at -80 ºC or lower until shipment to the EET Biobank.
   * 1. Blood Collection
        1. Collection of Blood in Streck cfDNA Tube *(Add number of tubes based upon total volume in Specimen Collection Table, assume 10 mL/tube)*
4. Label [number] 10 mL Streck cfDNA tubes according to the instructions in Section 5.4.2.
5. Collect 10 mL of blood into each pre-labeled tube and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen. *[Include the following language if patients may have an indwelling catheter:* heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, then venipuncture is recommended as a first choice collection method. If a Streck cfDNA tube immediately follows a heparin tube in the draw order, then collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT is recommended.]
6. **After collection, blood in Streck cfDNA tubes should never be refrigerated,** as this will compromise the specimen. Blood collected in Streck cfDNA tubes is stable at room temperature.
   * + 1. Collection of Blood in Red Top Tube for Serum Processing
7. Label red-top tube(s) according to the instructions in Section 5.4.2.
8. Collect 10 mL of blood in red-top tube.
9. Allow blood to clot upright at room temperature for at least 30 minutes (maximum 60 minutes) prior to processing. If the blood is not immediately processed after the clotting period, then tubes should be stored (after the 30-60 minutes of clotting time) at 4°C for no longer than 4 hours. Process serum from red top tubes by centrifuging for 10 minutes at 1,200 × g at room temperature.
10. **Using a clean transfer pipette,** aliquotserum into the labeled (using the label printed from the ETCTN Specimen Tracking System or following the instructions in Section 5.4.2) cryovials at an aliquot volume of 1 mL per tube. Avoid picking up red blood cells when aliquoting by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube. Tightly secure the cap of the vials before storage. Aliquoting and freezing of serum specimens should be completed within 1 hour of centrifugation.
11. Store serum cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to delivering to laboratory. Do not allow specimens to thaw after freezing.
    * + 1. Collection of Blood in [EDTA, Sodium Heparin, etc.] Tubes for Plasma Processing
12. Label EDTA tube(s) according to the instructions in Section 5.4.2.
13. Collect 10 mL of blood in EDTA (purple top) tube(s).
14. Process plasma by centrifuging for 10 minutes at 1,200 × g at room temperature.
15. Using a clean transfer pipette, transfer 1 mL of plasma into each of the labeled cryovials (using the label printed from the ETCTN Specimen Tracking System or following the instructions in Section 5.4.1). Avoid picking up the blood cells when aliquoting by keeping the pipet above the cell layers and leaving a small amount of plasma in the tube. Tightly secure the cap of the vials before storage. Aliquoting and freezing of plasma specimens should be completed within 1 hour of centrifugation.
16. Store plasma cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to delivering to laboratory. Do not allow specimens to thaw after freezing.
    * + 1. Collection of Blood in [EDTA, Sodium Heparin, etc.] Tubes for Shipping Whole Blood
17. Label EDTA tube(s) according to the instructions in Section 5.4.2.
18. Collect 10 mL blood in EDTA tube(s) and gently invert tube to mix.
19. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
20. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.
    * 1. Collection of Bone Marrow
         1. Collection of Bone Marrow in [EDTA, Sodium Heparin, etc.] Tubes for Shipping
21. Label [EDTA, sodium heparin] tube(s) according to the instructions in Section 5.4.2.
22. Collect 3-5 mL bone marrow in [EDTA, sodium heparin] tube(s) and gently invert tube to mix.
23. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
24. If bone marrow cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.
    * 1. Collection of Saliva [or Buccal Cells] for Shipping

***Patient should not eat, drink, smoke, or chew gum for 30 minutes prior to collection.***

1. Label tubes according to the instructions in Section 5.4.2.
2. Collect saliva [or buccal cells] according to manufacturer instructions. [*For Buccal Cell collections,* *add:* Rub the inside of the cheeks firmly, but do not pierce the skin or contaminate the swab with blood. Do not touch the teeth or other parts of the mouth when inserting or removing the swab.]
3. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
4. If saliva [or buccal cells] cannot be shipped on the day of collection (e.g., a late scheduled collection), then store according to manufacturer instructions.
   * 1. *Add additional sections as appropriate.*

## Shipping Specimens from Clinical Site to the EET Biobank

*This section should be kept if any specimens are being shipped to the EET Biobank. Standard procedures for packing specimens using EET Biobank-supplied kits (*e.g.*, ambient shipper, single-chamber kit, dual-chamber kit) can be found below. Shipping instructions will vary depending on the specimen types and time points. Below are options for standard language that can be used. Please use/modify these sections as appropriate for your study. Sections that are not relevant should be deleted.*

* + 1. General Shipping Information
       1. **Required Forms for Specimen Submissions** *(Edit the Table below to include only those rows relevant for the specimens being sent to the EET Biobank as shown in the Specimen Collection Table)*

| **Specimen** | **Required Forms** |
| --- | --- |
| Archival Tissue | 1. Shipping List 2. Anatomic Pathology Report corresponding to the tissue collection procedure |
| New Biopsy Tissue  *[Use this row for new research-only biopsies]* | 1. Shipping List 2. Tissue Biopsy Verification Form 3. Diagnostic Anatomic Pathology Report (i.e., most recent anatomic pathology report specifying the diagnosis) 4. Radiology and/or Operative Report |
| Surgical Tissue  *[Use this row for surgical tissue submitted in formalin, frozen, or fresh]* | 1. Shipping List 2. Tissue Biopsy Verification Form 3. Diagnostic Anatomic Pathology Report (i.e., most recent anatomic pathology report specifying the diagnosis) 4. Radiology and/or Operative Report 5. Corresponding Pathology Report from the surgery (if available)1   1If the Corresponding Pathology Report becomes available after shipment of specimens to the EET Biobank, then it must be sent to the EET Biobank via secure email and uploaded to Rave. |
| Surgical Tissue  *[Use this row for FFPE surgical tissue]* | 1. Shipping List 2. Corresponding Pathology Report from the surgery1   1For FFPE tissue, please hold submission of the tissue to the EET Biobank until the Corresponding Pathology Report is available. |
| Bone Marrow Aspirate or Biopsy | 1. Shipping List 2. Bone Marrow Report corresponding to the bone marrow collection procedure |
| Other (blood, blood product, urine, stool, etc.) [*modify this as appropriate for the specimens included in the study*] | 1. Shipping List |

**Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.**

Minimum required personally identifiable information:

* Remove patient identifiers such as name, date of birth, medical record number, social security number, and insurance information from the pathology or other clinical reports. [*Please note, this text may need to be revised if specimens are being routed to the EET Biobank for integral eligibility testing as information such as name and/or date of birth may be required for protocols that include testing that impacts patient care.]*
* Do not remove the date of procedure, surgical pathology ID (SPID) number, block number, and diagnosis.
  + 1. Specimen Shipping Instructions

When kits are provided, the shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container with ambient specimens.

Tissue in formalin must be shipped on the day of collection. Collect and ship on Monday through Wednesday.

Frozen specimens and archival (FFPE) tissue may be shipped on Monday through Thursday.

Fresh blood *[when applicable, also add: bone marrow, saliva, buccal cells, urine, etc.]* may be shipped on Monday through Friday. Please select “Saturday Delivery” when shipping fresh blood *[when applicable, also add: bone marrow, saliva, buccal cells, urine, etc.]* on a Friday.

* + - 1. Shipping of FFPE Blocks and Glass Slides

1. Before packaging blocks or slides, verify that each specimen is labeled according to Section 5.4.2.2.
2. Blocks should be placed in a hard-sided container, preferably a special block holder, to protect the specimen. Glass slides are to be placed in plastic slide holders. Place tissue paper on top of the separated slides prior to closing the slide holder to reduce slide movement during shipment.
3. Place the blocks or slides in a reinforced cardboard shipping box with appropriate packaging filler to minimize movement of specimens within the shipping box.
4. Include a copy of the forms listed above and a shipping manifest from the Specimen Tracking System with each shipment.
5. Please include a cold pack when shipping on hot days and extra insulation on cold days.
6. Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
   * + 1. Shipping Blood in an Ambient Shipper [*used for blood in Streck cfDNA tubes]*
7. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2.1 and that the lids of all primary receptacles containing liquid are tightly sealed.
8. Prepare the SAF-T-TEMP Gel Pak for shipment. **Note:** If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth. **Do not refrigerate, freeze, or microwave.**
9. Place the SAF-T-TEMP Pak in bottom of insulated chest. **Note:** The insulated chest must be shipped inside the provided cardboard box(es).
10. Place the blood collection tubes in zip-lock bags.
11. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
12. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
13. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
14. Place the lid on the insulated chest.
15. Close the outer flaps of the shipping box and tape shut.
16. Attach a shipping label to the top of the shipping container.
17. Attach an Exempt Human Specimen sticker to the side of the box.
18. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
    * + 1. Shipping Ambient Blood Using Supplies Provided by the Institution *[used when blood in EDTA or NaHep tubes are collected and shipped at ambient temperature at time points that Streck cfDNA tubes are not provided; this section can be modified for other liquid specimens shipped ambient, like urine]*
19. Before packaging specimens, verify that the collection tube is labeled according to instructions in section 5.4.2.1.
20. Place the blood collection tube into a zip-lock bag.
21. Place zip-lock bag into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
22. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
23. Place the specimen(s) and a copy of the shipping manifest into a sturdy shipping container. In winter months please use an insulated container and include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
24. Close the container and tape shut.
25. Attach a shipping label to the top of the shipping container.
26. Attach an Exempt Human Specimen sticker to the side of the container.
27. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
    * + 1. Shipping Ambient Tissue and Blood in a Single-Chamber Kit *[used when tissue in formalin is included at the same time points that blood other than blood in Streck cfDNA tubes is collected and shipped unprocessed at ambient temperature]*
28. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2 and that the lids of all primary receptacles containing liquid are tightly sealed. The lids of formalin jars should be wrapped in parafilm. Absorbent material must be placed around each primary container that holds liquid.
29. Place the specimens in zip-lock bags. Use a separate bag for each specimen type.
30. Place specimens into the secondary pressure vessel surrounded by bubble wrap. Place the lid on the secondary pressure vessel and set it inside the kit chamber.
31. Place a copy of the shipping manifest and corresponding reports such as pathology, operative, or radiology reports into the insulated shipping container.
32. Set the lid on top of the container. Close the outer flaps and tape shut.
33. Attach a shipping label to the top of the shipping container.
34. Attach an Exempt Human Specimen sticker to the side of the container.
35. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
    * + 1. Shipping Frozen Specimens in a Single-Chamber Kit *[used when frozen tissue is collected at time points when tissue is not collected in formalin]*
36. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2 and that lids of all primary receptacles containing liquid are tightly sealed.
37. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
38. Place the zip-lock bags in the biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
39. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
40. Place frozen specimens in the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
41. Insert a copy of the required forms into a plastic bag and place in the kit chamber.
42. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
43. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
44. Complete a FedEx air bill and attach to top of shipping container.
45. Complete a dry ice label.
46. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
47. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
    * + 1. Shipping Frozen Specimens Using Supplies Provided by the Institution *[used when frozen serum or plasma is collected, but not frozen tissue]*
48. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2 and that lids of all primary receptacles containing liquid are tightly sealed.
49. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
50. Place the zip-lock bags in a biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
51. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
52. Place frozen specimens into the insulated shipping container with dry ice. Layer the bottom of the container with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the container is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
53. Insert a copy of the required forms into a plastic bag and place in the shipping container.
54. Close the shipping container and tape it shut with durable sealing tape. Do not completely seal the container.
55. Complete a FedEx air bill and attach to top of shipping container.
56. Complete a dry ice label.
57. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
58. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
    * + 1. Shipping Frozen and Ambient Specimens in a Dual-Chamber Kit *[This version used when shipment includes tissue in formalin and frozen tissue]*

The Dual Chambered Specimen Procurement Kit is constructed to allow the shipment of frozen (on dry ice) and ambient (room temperature) specimens in the same container. **Dry ice may be placed in either compartment of the kit but should not be put in both.** The dual chambered kit is only used for shipments that contain both frozen and ambient specimens. If formalin-fixed tissue is shipped separately (not in the same shipment as frozen specimens), then it must be shipped using institutional shipping supplies.

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2 and that lids of all primary receptacles containing liquid are tightly sealed.
2. Pre-fill one of the kit chambers about 1/3 with dry ice.
3. Prepare the frozen specimens for shipment:
   1. Place the specimens into zip-lock bags.
   2. Place the zip-lock bags into a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the biohazard envelope.
   3. Put each biohazard envelope into a Tyvek envelope. Expel as much air as possible and then seal the Tyvek envelope.
4. Quickly place the Tyvek envelope containing frozen specimens in the kit compartment that is pre-filled with dry ice. Place the Tyvek envelope on top of the dry ice. Cover the specimens with additional dry ice until the compartment is almost completely full.
5. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
6. Prepare the ambient specimens for shipment:
   1. Seal the lids of the formalin jars with parafilm. Place absorbent material around the primary container of each liquid specimen. Place the specimens into zip-lock bags.
   2. Place specimens inside the secondary pressure vessel with bubble wrap.
   3. Secure the lid on the secondary pressure vessel and set it inside the kit chamber.
7. Insert a copy of the required forms in the kit chamber with the ambient specimens.
8. Place the Styrofoam lid on top of the kit compartment to secure specimens during shipment. Do not tape the inner chamber shut.
9. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
10. Complete a FedEx air bill and attach to top of shipping container.
11. Complete a dry ice label.
12. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
13. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.
    * + 1. Shipping Frozen and Ambient Specimens in a Dual-Chamber Kit *[This version used when shipment does not include tissue in formalin]*

The Dual-Chambered Specimen Procurement Kit is constructed to allow the shipment of frozen (on dry ice) and ambient (room temperature) specimens in the same container. **Dry ice may be placed in either compartment of the kit but should not be put in both.** The dual chambered kit is only used for shipments that contain both frozen and ambient specimens. If formalin-fixed tissue is shipped separately (not in the same shipment as frozen specimens), then it must be shipped using institutional shipping supplies.

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2 and that lids of all primary receptacles containing liquid are tightly sealed. If included in the shipment, formalin jar lids should be wrapped in parafilm.
2. Pre-fill one of the kit chambers about 1/3 with dry ice.
3. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type.
4. Two biohazard envelopes are provided so that ambient and frozen specimens can be packaged separately.
5. Place the zip-lock bags containing room temperature specimens in a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the zip-lock bags containing frozen specimens into the other biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
7. Put each secondary envelope into a Tyvek envelope. Expel as much air as possible and seal each envelope securely.
8. Quickly place the Tyvek envelope containing frozen specimens (*e.g.*, frozen tumor, serum, *etc.*) in the kit compartment that is pre-filled with dry ice. Place the Tyvek envelope on top of the dry ice. Cover the specimens with additional dry ice until the compartment is almost completely full.
9. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
10. Place the Tyvek envelope containing ambient temperature specimens (*e.g.*, formalin-fixed tissue) in the other kit compartment at room temperature.
11. Insert a copy of the required forms into a plastic bag and place in the kit chamber with the ambient specimens.
12. Place the Styrofoam lid on top of the kit compartment to secure specimens during shipment. Do not tape the inner chamber shut.
13. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
14. Complete a FedEx air bill and attach to top of shipping container.
15. Complete a dry ice label.
16. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
17. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

*[For solid tumor protocols, use the shipping address and contact information for assistance in Sections 5.6.3 and 5.6.4.]*

* + 1. Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank

The Research Institute at Nationwide Children's Hospital

700 Children's Drive, WA1340

Columbus, Ohio 43205

PH: (614) 722-2865

FAX: (614) 722-2897

E-mail: [BPCBank@nationwidechildrens.org](mailto:BPCBank@nationwidechildrens.org)

**FedEx Priority Overnight** service is very strongly preferred.

**NOTE:** The EET Biobank FedEx Account will not be provided to submitting institutions. There is no central Courier account for this study. Sites are responsible for the cost of shipments to the EET Biobank.

* + 1. Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank

PH: (614) 722-2865

E-mail: [BPCBank@nationwidechildrens.org](mailto:BPCBank@nationwidechildrens.org)

*[For leukemia protocols, use the shipping address and contact information for assistance in Sections 5.6.5 and 5.6.6.]*

* + 1. Shipping Address

Ship to the address below. Ship fresh blood and bone marrow specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank – Leukemia Division

Nationwide Children’s Hospital

700 Children’s Drive, C0825

Columbus, Ohio 43205

PH: (614) 722-3270

FAX: (614) 722-2856

E-mail:[BPCMGLab@nationwidechildrens.org](mailto:BPCMGLab@nationwidechildrens.org)

**FedEx Priority Overnight** service is very strongly preferred.

**NOTE:** The EET Biobank FedEx Account will not be provided to submitting institutions. There is no central Courier account for this study. Sites are responsible for the cost of shipments to the EET Biobank.

* + 1. Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank – Leukemia Division

Phone: (614) 722-3270

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## Shipping of Specimens from Clinical Site to Other Laboratories

*Provide explicit instructions about how clinical sites should ship specimens to each laboratory (other than the EET Biobank) listed in Section 5.1 Summary Table for Specimen Collection. A format for presentation of the required information is shown below.*

*If specimens will only be sent to the EET Biobank, these instructions and the subheadings below can be deleted and replaced with “N/A”.*

* + 1. Shipping of Specimens to *[Laboratory Name #1]*
       1. Specimen Shipping Instructions
       2. Shipping Address
       3. Contact Information for Assistance
    2. Shipping of Specimens to *[Laboratory Name #2]*
       1. Specimen Shipping Instructions
       2. Shipping Address
       3. Contact Information for Assistance

## Pharmacokinetic Studies

Pharmacokinetic (PK) studies will be done on all patients. At the Principal Investigator’s discretion, this requirement may be waived in case of patient hardship, including lack of venous access. In this event, patients will be replaced to ensure that adequate PK data are obtained for each group (*i.e*., at least 3 patients per group and at least 6 patients at the MTD level).

All PK measurements for this study will be performed and analyzed by *[Investigator/Institution OR Pharmaceutical Collaborator/Contractor]*. All data and results will be made available to the investigators on this study, to the industrial collaborator (if applicable), and to CTEP. The minimum turnaround time for PK measurements will be 4 weeks from receipt of samples by the analytical laboratory. In patients who experience unexpected serious toxicity or patients with gliomas or brain metastases taking anticonvulsant drugs, efforts will be made to have analysis available in 2 weeks. Availability of PK data is anticipated prior to dose escalation to another dose level.

PK sampling will be performed in Cycle 1 for all patients. In patients with incomplete PK from Cycle 1 and in those who change dose level or renal dysfunction group between cycles, repeat PK sampling is encouraged in subsequent cycles but is not mandatory.

If one or more of the major active metabolites of *[Study Agent]* is known to contribute at least 10% of the activity or toxicity observed, the PK of that/those metabolite(s) should also be measured.

Pharmacokinetic analytical methods are outlined in Section **9.5**.

* + 1. Specimen Collection / Documentation

Prior to drug administration on Day 1 of treatment, an indwelling heparin lock should be placed so that serial specimens can be collected. At each sampling time, 1 mL of blood will be withdrawn and discarded to assure that the solution used to maintain catheter patency does not dilute the sample. Even if a patient has a central venous catheter, it is preferable for Day 1 PK samples to be withdrawn through a peripheral heparin lock. However, if the patient objects or has problems with peripheral venous access, the central venous catheter may be used for PK sampling. In the event that the central venous catheter is used, sufficient blood should be withdrawn before each PK sample to assure that the solution used to maintain catheter patency does not dilute the PK sample. It is important to document whether the sample was collected through a heparin lock or central venous catheter, especially for day 1 sampling.

*Please provide complete instructions for documentation of sample acquisition**including source of samples (i.e., heparin lock or central catheter), as well as the method for labeling each sample with patient’s name (or unique identifier), sample date, scheduled sample collection time, and actual sample collection time.*

* + 1. Pharmacokinetic Sampling Schedule

*Please present a schedule for PK sample collection using the table format below. The appropriate number of time points (T1, T2, T3, etc.) and the times of sample collection (D1, D2, D3, etc.; 01:30, 02:00, 02:30, etc.) will be different for each agent. The possibility of impaired clearance rates should be considered in selection of PK sampling intervals.*

|  |  |
| --- | --- |
| **PK Time Point** | **Day hour:minute (h:m) of collection**  **(24-hour clock)** |
| T1 | D1 00:00 |
|  |  |
|  |  |
|  |  |
|  |  |

* + 1. Blood Sample Processing Procedures

*Please describe methods used to process samples for PK analysis here.*

* + 1. Shipping Instructions

*Please provide instructions and all procedures for shipping specimens to the central laboratory including the names of the responsible parties and contact information.*

## Biomarker Plan

*Use the table below to provide the study biomarker plan. The table should be divided by* ***tissue-based biomarkers****,* ***blood-based biomarkers****, and other specimen types if necessary. List the* ***priority*** *(1, 2, 3,* etc.*) by specimen type;* ***biomarker name*** *(*e.g.*, specific gene mutations, proteins, cells,* etc.*);* ***assay*** *(*e.g.*, whole exome sequencing [WES], RNA sequencing [RNA-Seq], immunohistochemistry [IHC], flow cytometry,* etc.*);* ***use in the trial*** *(*i.e.*, integral, integrated, or exploratory) and* ***purpose*** *(*e.g.*, for eligibility criterion, to correlate findings with response to agent[s],* etc.*); amount and type of* ***specimens tested*** *(*e.g.*, 1 fresh tumor tissue core [FFPE], 2 frozen tumor tissue cores, 1 × 10 mL blood in Streck tube,* etc. [*all specimens in Sections 5.1 and 5.2 should be accounted for in this table]); specimen* ***collection time points*** *(*e.g.*, baseline, post-progression, upon meeting a pre-specified efficacy endpoint,* etc.*); whether specimen collection is* ***“M” (mandatory) or “O” (optional)****; and name of* ***laboratory*** *conducting the assay and the* ***lab PI****. If the table from the LOI form or the Consensus Review is pasted into this section, please remove the NCI resource and funding columns. Also, please remove any reference to the Biomarker Review Requirement from the Assay Column (e.g., No Review Required, NCLN Approved, BRC Approved, NCLN Review Required, BRC Review Required, etc.).*

*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)*).*

*Note that integral biomarkers must be listed as mandatory, whereas integrated and exploratory biomarkers can be either mandatory or optional. Please see the following articles for guidance on determining when mandatory biopsies are appropriate: Ganti, A.K. (“Tissue Specimens in Clinical Trials: A Double-Edged Sword*.” The ASCO Post. *2017.) and Peppercorn* et al. *(“Ethics of Mandatory Research Biopsy for Correlative End Points Within Clinical Trials in Oncology*.” J Clin Oncol. *2010; 28:2635-40.).*

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

***Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing.***

| **Priority** | **Biomarker Name** | **Assay and**  **CLIA: Y/N** | **Use in the Trial and Purpose** | **Specimens Tested** | **Collection Time Points** | **Mandatory or Optional** | **Assay Laboratory, Lab PI and Lab PI Email** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Tissue-based** | | | | | | | |
| 1 | *[Add biomarker name]* | *[Add assay]*  CLIA: *[Yes or No]* | *Integral*  *[Describe assay purpose]* | *[Add tissue]* | *[Add collection time points]* | M | *[Add assay laboratory name, Lab PI and Lab PI Email]* |
| 2 | *[Add biomarker name]* | *[Add assay]*  CLIA: *[Yes or No]* | *Integrated*  *[Describe assay purpose]* | *[Add tissue]* | *[Add collectiontime points]* | *[Add M or O]* | *[Add assay laboratory name, Lab PI and Lab PI Email]* |
| 3 | *[Add biomarker name]* | *[Add assay]*  CLIA: *[Yes or No]* | *Exploratory*  *[Describe assay purpose]* | *[Add tissue]* | *[Add collectiontime points]* | *[Add M or O]* | *[Add assay laboratory name, Lab PI and Lab PI Email]* |
| **Blood-based Biomarkers** | | | | | | | |
| 1 | *[Add biomarker name]* | *[Add assay]*  CLIA: *Yes or No]* | *Integral*  *[Describe assay purpose]* | *[Add fluid]* | *[Add collection time points]* | *[Add M or O]* | *[Add assay laboratory name, Lab PI and Lab PI Email]* |
| 2 | *[Add biomarker name]* | *[Add assay]*  CLIA: *[Yes or No]* | *Integrated*  *[Describe assay purpose]* | *[Add fluid]* | *[Add collectiontime points]* | *[Add M or O]* | *[Add assay laboratory name, Lab PI and Lab PI Emal]* |
| 3 | *[Add biomarker name]* | *[Add assay]*  CLIA: *[Yes or No]* | *Exploratory*  *[Describe assay purpose]* | *[Add fluid]* | *[Add collectiontime points]* | *[Add M or O]* | *[Add assay laboratory name,Lab PI and Lab PI Email]* |
| ***[*Urine, Saliva, Stool *]*-based *(If biomarkers utilizing other specimen types are included, select appropriate header(s))*** | | | | | | | |
| 1 | *[Add biomarker name]* | *[Add assay]*  CLIA: *[Yes or No]* | *Integral*  *[Describe assay purpose]* | *[Add tissue/fluid]* | *[Add collection time points]* | *[Add M or O]* | *[Add assay laboratory name, Lab PI and Lab PI Email]* |
| 2 | *[Add biomarker name]* | *[Add assay]*  CLIA: *[Yes or No]* | *Integrated*  *[Describe assay purpose]* | *[Add tissue/fluid]* | *[Add collection time points]* | *[Add M or O]* | *[Add assay laboratory name, Lab PI and Lab PI Email]* |
| 3 | *[Add biomarker name]* | *[Add assay]*  CLIA: *[Yes or No]* | *Exploratory*  *[Describe assay purpose]* | *[Add tissue/fluid]* | *[Add collection time points]* | *[Add M or O]* | *[Add assay laboratory name, Lab PI and Lab PI Email]* |

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

***IMPORTANT:*** *Please refer to the LOI Consensus Review or other biomarker-related review documents to make sure that all requested information is* ***submitted to PIO*** *to support the biomarker plan for this study. For example:*

* *Any supporting materials that should be submitted to PIO for BRC review (*e.g., *Study Checklist for Early Phase Trials with CTEP-Supported Biomarker Assays, available at* [*http://ctep.cancer.gov/protocolDevelopment/docs/Study\_Checklist\_Early\_Phase\_Trials\_Biomarker\_Assays.docx*](http://ctep.cancer.gov/protocolDevelopment/docs/Study_Checklist_Early_Phase_Trials_Biomarker_Assays.docx)*, laboratory SOPs, published or unpublished data,* etc.*)*
* *A letter of commitment for a previously BRC-approved assay.*
* *Funding information, while not included in the protocol, should be communicated to CTEP in the response to the LOI Consensus Review.*

*If applicable, please also confirm that biomarker plan recommendations are addressed in your study protocol. For example:*

* *Biomarker Review Committee (BRC) recommendations;*
* *National Clinical Laboratory Network (NCLN) recommendations; or*
* *Center for Immune Monitoring and Analysis of Cancer (CIMAC) recommendations.*

*Please briefly describe each planned correlative study in the appropriate subsection(s) below. Also please see the “Guidelines for Correlative Studies in Clinical Trials” provided with the LOI response and available on the CTEP website (*[*https://ctep.cancer.gov/protocolDevelopment/templates\_applications.htm*](https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm)*;* [*http://ctep.cancer.gov/protocolDevelopment/ancillary\_correlatives.htm*](http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm)*). For each study, please provide information regarding the receipt and processing of specimens at the EET Biobank (if applicable) or the laboratory that will be receiving the specimens sent from the clinical site. Please also provide information about the laboratory conducting each correlative study. A format for presentation of the required information is shown below.*

## Integral Laboratory or Imaging Studies

*If the protocol includes any* ***integral*** *biomarker studies using* in situ *hybridization (ISH), immunohistochemistry (IHC), and/or DNA-based mutation assays, you may fill out the appropriate template (found at* [*https://cdp.cancer.gov/resources/templates.htm*](https://cdp.cancer.gov/resources/templates.htm)*) and attach to this protocol submission as separate Appendices (see Appendix F).*  ***ETCTN***  *trials requiring the use of patient specimens may insert the “Correlative Science Proposal Submission Form” for ETCTN studies into the protocol (this form can be found at* [*http://ctep.cancer.gov/protocolDevelopment/ancillary\_correlatives.htm*](http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm)*).*

*If the laboratory or laboratories performing the studies has an alternatively-formatted document that supplies the same level of information regarding validation, materials and methods,* etc*., it may be used instead of the templates.*

*In all cases, the laboratory’s Standard Operating Procedures (SOPs) for all integral assays should be submitted to CTEP with the initial protocol submission for review.*

* + 1. Title – Integral Laboratory Study #1
       1. Specimen(s) Receipt and Processing at the EET Biobank *[or other laboratory]*
       2. Site(s) Performing Correlative Study
       3. Shipment of Specimens from the EET Biobank to Site Performing Correlative Study *[only include for EET Biobank]*

Specimens will be shipped from the EET Biobank to:

*[insert laboratory shipping address]*

* + - 1. Contact Information for Notification of Specimen Shipment [From EET Biobank or initial receiving site to downstream lab; name of person/team receiving and email (can be a distribution list).  If lab receiving specimen directly, refer to section 5.7]
    1. Title – Integral Laboratory Study #2
       1. Specimen(s) Receipt and Processing at the EET Biobank *[or other laboratory]*
       2. Site(s) Performing Correlative Study
       3. Shipment of Specimens from the EET Biobank to Site Performing Correlative Study *[only include for EET Biobank]*

Specimens will be shipped from the EET Biobank to:

*[insert laboratory shipping address]*

* + - 1. Contact Information for Notification of Specimen Shipment *[From EET Biobank or initial receiving site to downstream lab; name of person/team receiving and email (can be a distribution list).  If lab is receiving specimen directly, refer to section 5.7]*

## 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. Specimen(s) Receipt and Processing at the EET Biobank *[or other laboratory]*
       2. Site(s) Performing Correlative Study
       3. Shipment of Specimens from the EET Biobank to Site Performing Correlative Study *[only include for EET Biobank]*

Specimens will be shipped from the EET Biobank to:

*[insert laboratory shipping address]*

* + - 1. Contact Information for Notification of Specimen Shipment [From EET Biobank or initial receiving site to downstream lab; name of person/team receiving and email (can be a distribution list).  If lab is receiving specimen directly, refer to section 5.7]
    1. Title – Integrated Laboratory Correlative Study #2
       1. Specimen(s) Receipt and Processing at the EET Biobank *[or other laboratory]*
       2. Site(s) Performing Correlative Study
       3. Shipment of specimens from the EET Biobank to Site Performing Correlative Study *[only include for EET Biobank]*

Specimens will be shipped from the EET Biobank to:

*[insert laboratory shipping address]*

* + - 1. Contact Information for Notification of Specimen Shipment [From EET Biobank or initial receiving site to downstream lab; name of person/team receiving and email (can be a distribution list).  If lab is receiving specimen directly, refer to section 5.7]

## Exploratory/Ancillary Correlative Studies

* + - 1. Title – Exploratory/Ancillary Laboratory Correlative Study #1
      2. Specimen(s) Receipt and Processing at the EET Biobank *[or other laboratory]*
      3. Site(s) Performing Correlative Study
      4. Shipment of specimens from the EET Biobank to Site Performing Correlative Study *[only include for EET Biobank]*

Specimens will be shipped from the EET Biobank to:

*[insert laboratory shipping address]*

* + - 1. Contact Information for Notification of Specimen Shipment [From EET Biobank or initial receiving site to downstream lab; name of person/team receiving and email (can be a distribution list).  If lab receiving specimen directly, refer to section 5.7]
    1. Title – Exploratory/Ancillary Laboratory Correlative Study #2
       1. Specimen(s) Receipt and Processing at the EET Biobank *[or other laboratory]*
       2. Site(s) Performing Correlative Study
       3. Shipment of Specimens from the EET Biobank to Site Performing Correlative Study *[only include for EET Biobank]*

Specimens will be shipped from the EET Biobank to:

*[insert laboratory shipping address]*

* + - 1. Contact Information for Notification of Specimen Shipment [From the EET Biobank or initial receiving site to downstream lab; name of person/team receiving and email (can be a distribution list).  If lab is receiving specimen directly, refer to section 5.7]

## 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 PLAN

## *[Hepatic]* Stratification by Hepatic Dysfunction

* + 1. Study Definition of Hepatic Dysfunction Groups

Patients entering this study will be stratified into four groups or cohorts (A: normal, B: mild dysfunction, C: moderate dysfunction, and D: severe dysfunction) according to their hepatic function, as outlined in the following table:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group**  **Liver Function** | **Group A**  **Normal** | **Group B**  **Mild** | **Group C**  **Moderate** | **Group D**  **Severe** |
| Total  Bilirubin | ≤ ULN | B1: ≤ ULN  B2: >1.0× – 1.5× ULN | >1.5× – 3× ULN | >3× ULN |
| SGOT/AST | ≤ ULN | B1: > ULN  B2: Any | Any | Any |

* Patients must fulfill both total bilirubin and SGOT/AST criteria to be included in a group. However, if a patient’s total bilirubin level and SGOT/AST level indicate different groups, the patient may be enrolled in the indicated group with the greatest degree of liver dysfunction.
* No distinction will be made between liver dysfunction due to metastases and liver dysfunction due to other causes.
* All liver function tests must be completed within 24 hours prior to the start of treatment.
* Group B (mild): For the purposes of this study, the “mild” liver dysfunction may be defined according to either of two criteria (B1 and B2), so that patients in Group B may come from either of these groups. Patients in Groups B1 and B2 are thus considered to have comparable liver dysfunction and will be combined for dose level allocation and all analyses.
* Patients whose degree of hepatic dysfunction changes (becomes worse or better) between registration and initiation of protocol therapy may be re-assigned to a different dysfunction group and dose level. This change should be discussed with the Principal Investigator. The Organ Dysfunction Working Group Coordinator must document reassignments with notification to Theradex.
* Group A (normal): Patients in group A are included in this study as control subjects and will be followed for toxicity; however, the definitions of DLT in Section 6.4 will not apply and a recommended dose will not be defined in these patients.
  + 1. Markers of Liver Dysfunction

Each patient’s liver dysfunction markers should be evaluated and documented at baseline and prior to each treatment cycle. See Appendix A for instructions.

## *[Renal]* Stratification by Renal Dysfunction

Patients entering this study will be stratified into up to five groups or cohorts (A: normal, B: mild dysfunction, C: moderate dysfunction, D: severe dysfunction, E: renal dialysis) according to their renal function, as outlined in the following table:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group**  **Renal Function** | **Group A** | **Group B** | **Group C** | **Group D** | **Group E** |
| **Normal** | **Mild\*** | **Moderate** | **Severe** | **Renal Dialysis** |
| **BSA-indexed eGFR\*\*** | ≥80\*\*\* | 50-79\*\*\* | 30-49\*\*\* | <30 | Any |

\* The Mild group will not enroll patients, unless tolerability or pharmacokinetic differences are observed between normal and Moderate cohorts.

\*\* The (BSA-indexed) eGFR is determined using the procedure described below.

\*\*\* Based on the 1998 FDA Guidance for Industry “Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling”

*Although historically kidney function in oncology patients has been determined using the Cockcroft-Gault formula, novel formula have been developed by the nephrology field to more accurately and precisely estimate GFR. Initially this was the MDRD equation, followed by (at the time of writing) the CKD-EPI equation, and it is expected that the standard for determining eGFR will keep improving the newer formula. Therefore, the kidney function of patients enrolled on oncology organ dysfunction trials should be ideally be evaluated with the most current standard available at initiation of study.*

*Several formulae have been used historically or developed more recently, and they are listed below in order of decreasing preference and supporting evidence. For each trial, a single formula should be selected and consistently applied for all patients.*

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, *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/1.73m2 and needs no further conversions.

1. Estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).

175 x SCr–1.154 x age–0.203 x 0.742 (if female) x 1.212 (if black)

Output is in mL/min/1.73m2 and needs no further conversions.

1. Estimated creatinine clearance (Clcr) by the Cockcroft-Gault (C-G) equation (Cockcroft *et al*., 1976).



Followed by conversion to a value normalized to 1.73m2 with the patient’s BSA.

* (BSA-indexed) eGFR should be calculated at baseline and prior to each treatment cycle.
* All renal function tests must be completed within 24 hours prior to the start of treatment.
* Group E (renal dialysis): Patients receiving renal dialysis should follow group D (severe) for dosing purposes.
* Patients whose degree of renal dysfunction changes (becomes worse or better) between registration and initiation of protocol therapy may be re-assigned to a different dysfunction group and dose level. This change should be discussed with the Principal Investigator.
* Group A (normal): Patients in Group A are included in this study as control subjects and will be followed for toxicity; however, the definitions of DLT in Section 6.4 will not apply and a recommended dose will not be defined in these patients.

## Agent Administration

*Please state the route and schedule of [CTEP IND Agent] administration. (For example, “Agent XXX is given intravenously as a 1-hour infusion on days 1, 3, and 5 of a 21-day cycle.”)*  Treatment will be administered on an *[inpatient/outpatient]* basis. To allow for *[hepatic/renal]* function testing within 24 hours before drug administration and maximum PK sampling within a standard working week, the first dose of *[CTEP IND Agent]* should be administered on a Tuesday. However, for those institutions with resources able to obtain PKs on weekends, treatment may be started on other days.

*Please state any special precautions or warnings relevant for agent administration (e.g., incompatibility of agent with commonly used intravenous solutions, necessity of administering agent with food, 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 Nomenclature and Expression.*

The patient’s starting dose will be assigned by the Organ Dysfunction Working Group Coordinator at the time of registration according to the schema and rules outlined in Section 6.5. The dose may be reduced for individual patients in subsequent cycles depending on toxicity (Section 7). In calculating surface areas, actual heights and weights should be used; that is, there should be no adjustment to “ideal” weight.

Reported adverse events and potential risks of *[CTEP IND Agent]* are described in Section 10.1. Appropriate dose modifications for *[CTEP IND Agent]* are described in Section 7.2. No investigational or commercial agents or therapies other than those described in Section 6 (Treatment Plan) may be administered with the intent to treat the patient’s malignancy.

## Definition of Dose-Limiting Toxicity

*Please provide explicit definitions of the type(s), grade(s), and duration(s) of all agent-specific dose-limiting adverse event(s) below. In addition, certain events will be defined as dose limiting for all organ dysfunction studies. Suggested text is provided below.*

The following treatment-related adverse events are considered dose limiting for all hepatic/renal dysfunction studies:

* Any > grade 3 non-hematologic toxicity (excluding alopecia, hypersensitivity, and liver abnormalities)
* Grade 4 neutropenia, or occurrence of neutropenic fever with ANC <1.5 x 109/L
* Grade 4 thrombocytopenia
* Grade 3 nausea and vomiting if it occurs despite maximal (5HT antagonist and corticosteroid) antiemetic therapy, and if hydration is required for >24 hours.
* Grade 3 diarrhea despite patient compliance with loperamide therapy.
* *[Hepatic only]* Liver toxicity:

Note: Investigators should use their best judgment based on clinical and radiological criteria to exclude progressive disease or other factors which may increase bilirubin as the cause of increased hepatic dysfunction.

- Patients in mild dysfunction group (Groups B1-2): increase of total bilirubin to level defined for the severe group lasting >2 weeks.

- Patients in moderate dysfunction group (Group C): 1.5× increase from baseline total bilirubin to level defined for the severe group lasting for >2 weeks.  
(Note: 1.5× increase from baseline total bilirubin which does not put a patient in the severe group does not constitute a DLT.)

- Patients in severe dysfunction group (Group D): 1.5× increase from baseline without recovery to <1.2× baseline value of total bilirubin for >2 weeks.

* *[Renal only]* Renal toxicity:

- If opened to accrual: Patients in mild dysfunction group (Group B): decrease to <66% of baseline eGFR lasting >2 weeks.

- Patients in moderate dysfunction group (Group C): decrease to <66% of baseline eGFR, lasting for >2 weeks

- Patients in severe dysfunction group (Group D): decrease to <66% of baseline eGFR, for >2 weeks.

* *[Hepatic]* In patients with biliary stents, elevations of total bilirubin and SGOT that are due to obstructed biliary stents or cholangitis not accompanied by neutropenia will not be considered as a DLT.
* *[Renal]* In patients undergoing renal dialysis, laboratory parameters related to renal function that are known to worsen between dialysis treatments will not be considered as DLTs.
* Treatment delays of ≥2 weeks due to treatment-related toxicity will constitute a DLT.

*[Renal]* Elevations of electrolyte, BUN, and creatinine levels will not be considered in determination of the DLT unless they are known toxicities of *[CTEP IND Agent]*. They will be attributed to the patient’s primary renal failure. However, if sudden changes in these parameters occur in a temporal relationship to administration of *[CTEP IND Agent]*, the changes should be attributed to *[CTEP IND Agent]* and considered in the determination of DLT, MTD, and dosing recommendations.

Management and dose modifications associated with the above adverse events are outlined in Section 7. Dose escalation will proceed within each group according to the rules stated below.

## Dose-Escalation Scheme (Hepatic Dysfunction)

*Please state route and schedule of Study Agent administration, and enter exact doses for each dose level and group in the table below. (For example, “Agent XXX is given intravenously as a 1-hour infusion on days 1, 3, and 5 of a 21-day cycle.)*

*[CTEP IND Agent]* is given *[route/duration]* on *[day/days]* of a *[#]-day* cycle.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Group A** | **Group B** | **Group C** | **Group D** |
| **Dose**  **Level** | **Normal liver function** (*units)* **\*** | **Mild liver dysfunction** (*units)* \* | **Moderate liver dysfunction** (*units)* \* | **Severe liver dysfunction** (*units)* \* |
| **Level -1** |  |  |  |  |
| **Level 1** |  |  |  |  |
| **Level 2** |  |  |  |  |
| **Level 3** |  |  |  |  |
| **Level 4** |  |  |  |  |

*\* Doses are stated as exact dose in units (e.g., mg/m2, mcg/kg, etc.) rather than as a percentage.*

*\*\* See Section 5.1 for the Group E dosing scheme.*

* See Section 6.1.1 for definitions of liver dysfunction groups.
* The first cohort of patients will be treated at dose level 1. Dose level –1 is only to be used if dose reduction is necessary.
* The following modifications to the usual “3&3” dose escalation scheme allow for the dosing of new patients in the event that not all patients treated at a current dose level are yet evaluable for toxicity.
  + 1. Dose Escalation Rules
* Dose escalation will proceed within each hepatic dysfunction group according to the scheme outlined in Section 6.5. DLT is defined above (Section 6.4).
* Only DLTs that occur during the first cycle of treatment will be used to guide dose escalation.
* Patients are considered evaluable for toxicity when they have received one cycle of therapy (the planned dose or duration of agent treatment) and have either 1) experienced DLT or 2) been followed for one full cycle without DLT.
  + 1. Dose Escalation Definitions
* The MTD is the highest dose at which no more than one instance of DLT is observed (among 6 patients treated). This is also the recommended dose (RD) for further study.
* L denotes the current dose level in a given hepatic dysfunction group. When patients are active in cycle 1 at two dose levels in the same group concurrently, L will denote the lower dose level.
  + 1. Dose Level Sample Size
* Accrual at each dose level of each hepatic dysfunction group will proceed up to a maximum of 6 patients subject to the following rules provided the MTD has not been determined:

|  |  |
| --- | --- |
| No DLT has occurred at dose level L among 1-2 evaluable patients | Accrual continues at dose level L up to 6 patients. |
| No DLT has occurred at dose level L among 3-4 evaluable patients | Accrual to dose level L is suspended and up to 3 patients may be accrued to level L+1 during this suspension. |
| No DLT has occurred at dose level L among 5 evaluable patients | Accrual to dose level L is terminated and accrual to the next dose level proceeds. |
| 1 DLT has occurred at dose level L | 6 patients will be accrued to L. |
| 2 DLTs have occurred at a dose level. | That dose level exceeds the MTD and no additional patients will be treated at that dose level or higher. |

* Patients who are not evaluable for DLT should be replaced, including those taking enzyme-inducing anticonvulsant drugs whose PK values (increased clearance/decreased AUC) suggest interaction with CYP450 isoenzymes.
* Once the MTD has been determined for a given hepatic dysfunction group, a maximum of 12 patients may be accrued to this dose level.
  + 1. Dose Level Assignment

**Before determination of the MTD:**

|  |  |  |  |
| --- | --- | --- | --- |
| **# pts evaluable for toxicity at L** | **# pts with DLT at L** | **MTD Status** | **Dose level assignment for**  **new patient** |
| <3 | 0-1 | Not yet defined | L (up to 6 pts) |
| ≥2 | MTD exceeded | Fill L-1 (to 6 pts) |
| 3-4 | 0 | Not yet defined | L+1 (to 3 pts) |
| 1 | Not yet defined | L (up to 6 pts) |
| ≥2 | MTD exceeded | Fill L-1 (to 6 pts) |
| 5 | 0 | ≤ MTD | L+1 |
| 1 | Not yet defined | L (up to 6 pts) |
| ≥2 | MTD exceeded | Fill L-1 (to 6 pts) |
| 6 | 0-1 | ≤ MTD | L+1 |
| ≥2 | MTD exceeded | Fill L-1 (to 6 pts) |

* Patients whose degree of hepatic dysfunction changes (becomes worse or better) between registration and initiation of protocol therapy may be re-assigned to a different dysfunction group and dose level. This change should be discussed with the Principal Investigator and must be documented with the Organ Dysfunction Working Group Coordinator. (For patients whose degree of hepatic dysfunction changes after initiation of therapy, see Section 6.1.)
* A maximum of 3 patients may be assigned to L+1 during the suspension of accrual to level L (3-4 patients evaluable on L with no observed toxicity). When 1 or more patients have been assigned to L+1, the following rules apply:

|  |  |
| --- | --- |
| **# pts with DLT at L+1** | **Dose level assignment for new patient** |
| 0 | Accrual continues to L+1 up to 3 patients. |
| 1 | Accrue no additional patients to L+1 until all patients treated at L are evaluable. |
| >2 | The MTD has been exceeded at L+1. |

* Accrual to L need not be resumed (even if <6 patients have been accrued) provided no DLTs have been observed on L and <2 DLTs have been observed on L+1.

**After determination of the MTD:**

When the MTD has been determined, it may be expanded to a total of 12 patients according to patient availability. Based on the results from these additional patients, the MTD may be adjusted as follows:

|  |  |
| --- | --- |
| **# pts with DLT at MTD** | **Action** |
| <1/3 | The MTD (also the RD) remains the same for this hepatic dysfunction group. |
| >1/3 | Lower dose levels should be further studied in descending order to re-establish an appropriate MTD. |

* + 1. Maintaining Consistent Dosing Across the Hepatic Dysfunction Groups

In general, results from each hepatic dysfunction group will have implications for the other groups based upon the assumption that at any given dose level, the dysfunction-toxicity response gradient is monotonic. In other words, patients in a particular group will not tolerate a dose not tolerated by a group with lesser dysfunction and conversely, will tolerate a dose tolerated by a group with greater dysfunction. When discrepancies arise between observed results and this principle, they will be resolved in the direction of conservative practice. That is, the lower dose will be recommended for both groups if a higher dose is tolerated in a group of greater dysfunction, but not in the group of lesser dysfunction. In particular, dose level assignments and MTD determination will be made consistent across the various hepatic dysfunction groups as follows:

|  |  |
| --- | --- |
| **Observation for a particular dysfunction group** | **Action within other dysfunction groups** |
| MTD has been exceeded at a particular dose level | Accrual at that dose level or higher is terminated for all groups with greater dysfunction. |
| MTD has been established (including results of additional patients up to 12) at a particular dose level. | Accrual at lower dose levels is terminated for all groups with lesser dysfunction. |
| MTD has been established (including results of additional patients up to 12) at a particular dose level L while simultaneously, the MTD has been exceeded at that dose level in a group of lesser dysfunction. | The MTD is determined to be L-1 in both groups, and in both groups, there may be additional accrual (up to 12 patients) at dose level L-1, as described in 5.4.4. |

## Dose-Escalation Scheme (Renal Dysfunction)

*Please state route and schedule of Study Agent administration, and enter exact doses for each dose level and group in the table below. (For example, “Agent XXX is given intravenously as a 1-hour infusion on days 1, 3, and 5 of a 21-day cycle.)*

*[CTEP IND Agent]* is given *[route/duration]* on *[day/days]* of a *[#]-day* cycle.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Group A** | **Group B** | **Group C** | **Group D** | **Group E** |
| **Dose**  **Level** | **Normal Renal function** (*units)* \* | **Mild renal dysfunction**  (*units)* \* | **Moderate renal dysfunction**  (*units)* **\*** | **Severe renal dysfunction**  (*units)*  **\*** | **Kidney dialysis**  (*units)* \* |
| **Level -1** |  | TBD\*\* |  |  | \*\*\* |
| **Level 1** |  | TBD\*\* |  |  | \*\*\* |
| **Level 2** |  | TBD\*\* |  |  | \*\*\* |
| **Level 3** |  | TBD\*\* |  |  | \*\*\* |
| **Level 4** |  | TBD\*\* |  |  | \*\*\* |
| *\* Doses are stated as exact dose in clinically utilized units (e.g., mg/m2, mcg/kg, etc.) rather than as a percentage.*  *\*\** *To be determined based on the safety data available for Normal and Moderate at the time that this group potentially would be activated for enrollment* | | | | | |

\*\*\* See Section 6.2 for the Group E dosing scheme.

* See Section 6.2 for definitions of renal dysfunction groups.
* The first cohort of patients will be treated at dose level 1. Dose level –1 is only to be used if dose reduction is necessary.
* The following modifications to the usual “3&3” dose escalation scheme allow for the dosing of new patients in the event that not all patients treated at a current dose level are yet evaluable for toxicity.
  + 1. Dose Escalation Rules
* Dose escalation will proceed within each renal dysfunction group according to the scheme outlined in Section 6.6. DLT is defined above (Section 6.4).
* Only DLTs that occur during the first cycle of treatment will be used to guide dose escalation.
* Patients are considered evaluable for toxicity when they have received the planned dose or duration of therapy and have either 1) experienced DLT or 2) been followed for one full cycle without DLT.
  + 1. Dose Escalation Definitions
* The MTD is the highest dose at which no more than one instance of DLT is observed (among 6 patients treated). This is also the recommended dose (RD) for further study.
* L denotes the current dose level in a given renal dysfunction group. When patients are active in cycle 1 at two dose levels in the same group concurrently, L will denote the lower dose level.
  + 1. Dose Level Sample Size
* Accrual at each dose level of each renal dysfunction group will proceed up to a maximum of 6 patients subject to the following rules, provided the MTD has not been determined:

|  |  |
| --- | --- |
| No DLT has occurred at dose level L among 1-2 evaluable patients | Accrual continues at dose level L up to 6 patients. |
| No DLT has occurred at dose level L among 3-4 evaluable patients | Accrual to dose level L is suspended and up to 3 patients may be accrued to level L+1 during this suspension. |
| No DLT has occurred at dose level L among 5 evaluable patients | Accrual to dose level L is terminated and accrual to the next dose level proceeds. |
| 1 DLT has occurred at dose level L | 6 patients will be accrued to L. |
| 2 DLTs have occurred at a dose level. | That dose level exceeds the MTD and no additional patients will be treated at that dose level or higher. |

* Patients who are not evaluable for DLT should be replaced, including those taking enzyme-inducing anticonvulsant drugs whose PK values (increased clearance/decreased AUC) suggest interaction with CYP450 isoenzymes.
* Once the MTD has been determined for a given renal dysfunction group, a maximum of 12 patients may be accrued to this dose level.
  + 1. Dose Level Assignment

**Before determination of the MTD:**

|  |  |  |  |
| --- | --- | --- | --- |
| **# pts evaluable for toxicity at L** | **# pts with DLT at L** | **MTD status** | **Dose level assignment for**  **new patient** |
| <3 | 0-1 | Not yet defined | L (up to 6 pts) |
| ≥2 | MTD exceeded | Fill L-1 (to 6 pts) |
| 3-4 | 0 | Not yet defined | L+1 (to 3 pts) |
| 1 | Not yet defined | L (up to 6 pts) |
| ≥2 | MTD exceeded | Fill L-1 (to 6 pts) |
| 5 | 0 | ≤ MTD | L+1 |
| 1 | Not yet defined | L (up to 6 pts) |
| ≥2 | MTD exceeded | Fill L-1 (to 6 pts) |
| 6 | 0-1 | ≤ MTD | L+1 |
| ≥2 | MTD exceeded | Fill L-1 (to 6 pts) |

* Patients whose degree of renal dysfunction changes (becomes worse or better) between registration and initiation of protocol therapy may be re-assigned to a different dysfunction group and dose level. This change should be discussed with the Principal Investigator and must be documented with the Organ Dysfunction Working Group Coordinator. (For patients whose degree of renal dysfunction changes after initiation of therapy, see Section 6.2.)
* A maximum of 3 patients may be assigned to L+1 during the suspension of accrual to level L (3-4 patients evaluable on L with no observed toxicity). When 1 or more patients have been assigned to L+1, the following rules apply:

|  |  |
| --- | --- |
| **# pts with DLT at L+1** | **Dose level assignment for new patient** |
| 0 | Accrual continues to L+1 up to 3 patients. |
| 1 | Accrue no additional patients to L+1 until all patients treated at L are evaluable. |
| ≥2 | The MTD has been exceeded at L+1. |

**After determination of the MTD:**

When the MTD has been determined, it may be expanded to a total of 12 patients according to patient availability. Based on the results from these additional patients, the MTD may be adjusted as follows:

|  |  |
| --- | --- |
| **# pts with DLT at MTD** | **Action** |
| <1/3 | The MTD (also the RD) remains the same for this renal dysfunction group. |
| ≥1/3 | Lower dose levels should be further studied in descending order to re-establish an appropriate MTD. |

* + 1. Maintaining Consistent Dosing Across the Renal Dysfunction Groups

In general, results from each renal dysfunction group will have implications for the other groups based upon the assumption that at any given dose level, the dysfunction-toxicity response gradient is monotonic. In other words, patients in a particular group will not tolerate a dose not tolerated by a group with lesser dysfunction and conversely, will tolerate a dose tolerated by a group with greater dysfunction. When discrepancies arise between observed results and this principle, they will be resolved in the direction of conservative practice. That is, the lower dose will be recommended for both groups if a higher dose is tolerated in a group of greater dysfunction, but not in the group of lesser dysfunction. In particular, dose level assignments and MTD determination will be made consistent across the various renal dysfunction groups as follows:

|  |  |
| --- | --- |
| **Observation for a particular dysfunction group** | **Action within other dysfunction groups** |
| MTD has been exceeded at a particular dose level | Accrual at that dose level or higher is terminated for all groups with greater dysfunction. |
| MTD has been established (including results of additional patients up to 12) at a particular dose level. | Accrual at lower dose levels is terminated for all groups with lesser dysfunction. |
| MTD has been established (including results of additional patients up to 12) at a particular dose level L while simultaneously, the MTD has been exceeded at that dose level in a group of lesser dysfunction. | The MTD is determined to be L-1 in both groups, and in both groups, there may be additional accrual (up to 12 patients) at dose level L-1, as described in 5.4.4. |

## General Concomitant Medication and Supportive Care Guidelines

*Please state guidelines for use of concomitant medications or any additional appropriate supportive care medications or treatments. Also state if FDA-approved biosimilar growth factors are acceptable or not acceptable according to institutional policies. Specifically:*

* *[Hepatic]* Patients should be cautioned about the concomitant use of acetaminophen (Tylenol®, Percocet®, or other analgesic combination tablets containing acetaminophen).
* *[Renal]* Patients should be cautioned about the concomitant use of cimetidine, trimethoprim, or other agents that interfere with creatinine secretion or the creatinine assay.
* *Please indicate any other medications that should be avoided during this evaluation of [CTEP IND Agent]* *in patients with organ dysfunction.*
* *Potential drug interactions must be addressed for all agents to be used in this study, including commercial agents. Please refer to the appropriate FDA product label for any commercial agent(s) being used on this study.*
* *For agents known to be metabolized in the liver, please include appropriate information regarding the concurrent use of any medication or therapy with the potential to affect cytochrome P450 isoenzymes. Suggested text is provided below. This text should be deleted for studies of agents with no known hepatic metabolism.*

Because there is a potential for interaction of *[CTEP IND Agent]* with concomitantly administered drugs through the cytochrome P450 system, the case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect the P450 isoenzymes. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.Appendix F (Patient Drug Interactions Handout and Wallet Card) should be provided to patients if available.

## 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
* 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.
* The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
* Termination of the study by sponsor
* 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 Case Report Form (CRF).

## Duration of Follow-Up

Patients will be followed for *[# 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.

# DOSING DELAYS/DOSE MODIFICATIONS

## Retreatment Criteria

Prior to administration of each new cycle following Cycle 1, patients must have recovered the following organ function:

* absolute neutrophil count ≥1.5 × 109/L
* platelets ≥100 × 109/L
* total bilirubin *[Renal]* within normal institutional limits OR *[Hepatic]* normalized to the level of hepatic function defined by the cohort to which the patient was enrolled. (Note: For patients without a categorical change in bilirubin (including patients entered in the severe cohort), but an increase in tital bilirubin to ≥1.5-times baseline, treatment may resume when the level decreases to <1.2-times baseline.)
* AST (SGOT) / ALT (SGPT) *[Renal]* ≤3 × institutional upper limit of normal OR *[Hepatic]* normalized to the level of hepatic function defined by the cohort to which the patient was enrolled
* creatinine *[Hepatic]* ≤1.5 × upper limit of normal OR *[Renal]* normalized to the level of renal function defined by the cohort to which the patient was enrolled
* other (including neuropathy) Grade 0-1

**Laboratory evaluations (hepatic function tests) must be repeated within 24 hours prior to initiation of each cycle of therapy.** Patients not fulfilling these criteria should have treatment delayed by 1 week to allow for recovery of organ function. Patients who cannot be retreated within 2 weeks of the end of the previous cycle should be removed from study.

Recovery of baseline *[hepatic/renal]* function is NOT required prior to retreatment provided the decline is considered disease-related. However, patients who have *[CTEP IND Agent]*-induced deterioration of hepatic function should not be retreated and should be removed from the study.

For patients whose *[hepatic/renal]* dysfunction has changed (improved or deteriorated) since the last cycle, assignment to a different dose level and/or group or cohort may be appropriate following consultation with the Principal Investigator. All such changes must be documented with the Organ Dysfunction Working Group Coordinator.

## Dose Modification Guidelines

The dose of *[CTEP IND Agent]* prescribed for cycles subsequent to cycle 1 will be determined by the following guidelines that integrate the patient’s tolerance for the dose received in the previous cycle and the current dose level (L) for the patient’s *[hepatic/renal]* function group at the time of retreatment:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *[Hepatic]* **Dose Modification for Patients with Hepatic Dysfunction1** | | | | |
|  | **Worst toxicity in previous cycle** | | | |
| **1 or more of:**  **G2 \_*(non-heme tox)*** *\**  **persistent at D \_*(cycle length)*\_**  **G3 \_(*non-heme tox)*** *\**  **G4 non-heme (other)**  **Septic shock**  **Dose delay (> 2 wks)** | **1 or more of:**  **G2 \_*(non-heme tox)*** *\**  **recovered to G1 by D \_*(cycle length)*\_**  **G3 non-heme (other)**  **G4 heme**  **Febrile neutropenia**  **Hepatic DLT**  **Dose delay (­< 2 wks)** | **1 or more of:**  **G1 \_*(non-heme tox)*** *\** **G2 non-heme (other)**  **G3 heme**  **Dose delay (­< 1 wk)** | **All of:**  **G0 \_*(non-heme tox)*** *\**  **G0-1 non-heme (other)**  **G0-2 heme**  **No dose delay** |
| **Stable or improved**  **Hepatic Function** | Off study | Administer LOWER of:  Current dose level for current group  **OR**  \_\_*Dose\*\*\_\_* less than previous cycle | Administer LOWER of:  Current dose level for current group  **OR**  Same dose as previous cycle | Administer LOWER of:  Current dose level for current group  **OR**  \_\_*Dose\*\*\_\_* more than previous cycle |
| **Deteriorated**  **Hepatic Function**  **(1 group; *e.g*. from Group B to Group C)** | Off study | Off study | Administer LOWER of:  Current dose level for current group  **OR**  \_\_*Dose\*\*\_\_*less than previous cycle | Administer LOWER of:  Current dose level for current group  **OR**  Same dose as previous  cycle |
| **Deteriorated**  **Hepatic Function**  **(2 groups; *e.g*. from Group B to Group D)** | Off study | Off study | Off study | Administer LOWER of:  Current dose level for current group  **OR**  \_\_*Dose\*\*\_\_* less than previous cycle |

**1** This table can be modified to align with the drug-specific dose modifications and should be verified with the IDB Physician and sponsor.

*\* Please replace “non-heme tox” with the appropriate toxicity category (*e.g.*, neurologic) for agents with a known non-hematologic DLT (previously determined in patients with normal hepatic function). The term “ (non-heme tox) \*” under the worst toxicity criteria should be deleted for agents with a hematologic DLT.*

*\*\* State an exact dose in units (*e.g.*, mg/m2, mcg/kg, etc.) by which to lower or raise the dose of the previous cycle rather than a percentage.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *[Renal]* **Dose Modification for Patients with Renal Dysfunction** | | | | |
|  | **Worst toxicity in previous cycle** | | | |
| **1 or more of:**  **G2 \_*(non-heme tox)*** *\**  **persistent at D \_*(cycle length)*\_**  **G3 \_(*non-heme tox)*** *\**  **G4 non-heme (other)**  **Septic shock**  **Dose delay (> 2 wks)** | **1 or more of:**  **G2 \_*(non-heme tox)*** *\**  **recovered to G1 by D \_*(cycle length)*\_**  **G3 non-heme (other)**  **G4 heme**  **Febrile neutropenia**  **Renal DLT**  **Dose delay (­< 2 wks)** | **1 or more of:**  **G1 \_*(non-heme tox)*** *\**  **G2 non-heme (other)**  **G3 heme**  **Dose delay (­< 1 wk)** | **All of:**  **G0-1 non-heme (other)**  **G0-2 heme**  **No dose delay** |
| **Stable or improved**  **Renal Function** | Off study | Administer LOWER of:  Current dose level for current group  **OR**  \_\_*Dose\*\*\_\_* less than previous cycle | Administer LOWER of:  Current dose level for current group  **OR**  Same dose as previous cycle | Administer LOWER of:  Current dose level for current group  **OR**  \_\_*Dose\*\*\_\_* more than previous cycle |
| **Deteriorated**  **Renal Function**  **(1 group; *e.g*., from Group B to Group C)** | Off study | Off study | Administer LOWER of:  Current dose level for current group  **OR**  \_\_*Dose\*\*\_\_*less than previous cycle | Administer LOWER of:  Current dose level for current group  **OR**  Same dose as previous  cycle |
| **Deteriorated**  **Renal Function**  **(2 groups; *e.g*., from Group B to Group D)** | Off study | Off study | Off study | Administer LOWER of:  Current dose level for current group  **OR**  \_\_*Dose\*\*\_\_* less than previous cycle |

**1** This table can be modified to align with the drug-specific dose modifications and should be verified with the IDB Physician and sponsor.

*\* Please replace “non-heme tox” with the appropriate toxicity category (*e.g.*, neurologic, metabolic, etc.) for agents with a known non-hematologic DLT (previously determined in patients with normal renal function). The term “ (non-heme tox) \*” under the worst toxicity criteria should be deleted for agents with a hematologic DLT.*

* Patients should thus be retreated at the current dose level for the *[hepatic/renal]* dysfunction group that they fall into on the day of retreatment, unless toxicity in the previous cycle dictates that a lower dose be used (see table). The current dose level (L) is defined in Section 6.
* Collection of pharmacokinetics from patients who change dose level and/or *[hepatic/renal]* dysfunction group between cycles is encouraged but not mandatory.
* No patient should have his/her dose re-escalated following dose reduction for toxicity.
* The Principal Investigator or Study Coordinator should confirm the appropriate dose level prior to each cycle.

# PHARMACEUTICAL 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.*

## CTEP IND Agent(s)

***Confidential*** *pharmaceutical information for investigational study agents supplied by CTEP will be provided as attachments to the approved Letter of Intent (LOI) response and should be inserted below as indicated.*

* + 1. CTEP IND Agent #1 (NSC #)

*Insert pharmaceutical information for CTEP IND Agent here.*

**Availability**

*[CTEP IND Agent #1]* is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

*If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent’s Collaborative Agreement status will be provided in the approved LOI response letter.*

*[CTEP IND Agent #1]* is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

* + 1. CTEP IND Agent #2 (NSC #)

*Insert pharmaceutical information for CTEP IND Agent here. If only a single CTEP and/or CIP IND Agent will be used in the trial, this section (8.1.2) should be deleted.*

**Availability**

*[CTEP IND Agent #2]* is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

*If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent’s Collaborative Agreement status will be provided in the approved LOI response letter.*

*[CTEP IND Agent #2]* is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

* + 1. Agent Ordering and Agent Accountability
       1. NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

The CTEP Pharmaceutical Management Branch (PMB) will provide direction as to when sites can order PMB-supplied agents.

Submit agent requests through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time or use the dialog function in AURORA to communicate with PMB staff. Refer to the PMB’s website for specific policies and guidelines related to agent management.

* + - 1. Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a complete accountability of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Product Quality Complaint (PQC): A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) or by using the dialog function in AURORA to communicate with PMB staff.

* + 1. Material Safety Data Sheets
* The current versions of the material safety data sheets (MSDS or SDS) for PMB-distributed agents will be accessible to site investigators and research staff through the PMB AURORA application. Questions about MSDS access may be directed to the PMB at [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) or by using the dialog function in AURORA to communicate with PMB staff.
  + 1. Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, the maintenance of an “active” account status, a “current” password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

* + 1. Useful Links and Contacts
  + CTEP Forms, Templates, Documents: <http://ctep.cancer.gov/forms/>
  + NCI CTEP Investigator Registration: [RCRHelpDesk@nih.gov](mailto:RCRHelpDesk@nih.gov)
  + PMB policies and guidelines: <http://ctep.cancer.gov/branches/pmb/agent_management.htm>
  + PMB AURORA application: <https://ctepcore.nci.nih.gov/aurora/login>
  + CTEP Identity and Access Management (IAM) account: <https://ctepcore.nci.nih.gov/iam/>
  + CTEP IAM account help: [ctepreghelp@ctep.nci.nih.gov](mailto:ctepreghelp@ctep.nci.nih.gov)
  + IB Coordinator: [IBCoordinator@mail.nih.gov](mailto:IBCoordinator@mail.nih.gov)
  + PMB email: [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov)
  + PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

## 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.*

## Commercial Agent(s)

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

*Please indicate if FDA-approved biosimilar agents are acceptable or not acceptable in place of the reference product when used in standard-of-care regimens.*

*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.*

**Commercial Agent Shortages**

Specific guidance on how to address agent shortages for patients already enrolled on a clinical study as well as how to manage potential enrollment of new patients is provided at <https://ctep.cancer.gov/branches/pmb/drug_shortages.htm>.

Treatment plan modifications being made to avoid immediate hazard to patients is permissible under the Department of Health and Human Services (HHS) regulations at 45 CFR 46.108(a)(3)(iii). In accordance with HHS regulations, local investigators must promptly inform the IRB of record of this unanticipated problem and the management plan for the trial.

# STATISTICAL CONSIDERATIONS

## Study Design

This phase 1 trial will use a design involving five parallel groups or cohorts of patients with different degrees of *[hepatic/renal]* dysfunction.

* The dose escalation rules used in this study, as detailed in Section 6.4.1, are adapted from the standard up-and-down “3&3” design, and maintain the basic principles of that design. The design has been modified for this organ dysfunction study to eliminate waiting periods between dose levels as the clinical stability of patients with impaired *[hepatic/renal]* function is frequently limited, and it is thus unreasonable to delay therapy for 2-3 weeks in this patient population. The disadvantage of this approach is that it may increase the number of patients who receive a dose that is subsequently found to be above the recommended dose level. However, the benefit is expected to outweigh this risk as this population of patients is small, has few or no standard therapeutic options, and these patients usually have a limited timeframe during which therapy can be safely administered.
* Although dose-finding will be carried out independently for each of the liver dysfunction groups, an ancillary constraint is imposed: the dose recommended for a group with greater *[hepatic/renal]* dysfunction cannot be greater than that for a group with a lesser dysfunction. Section 6.4 describes how this constraint will be applied. While it is conceivable that patients with greater liver dysfunction might tolerate the study drug better than those with lesser dysfunction, it is considered very unlikely. Furthermore, the highest dose to be explored is no greater than the recommended dose for patients with normal liver function. Thus, the ancillary constraint can do no harm; it is intended to compensate in part for patient heterogeneity and yield more accurate final recommended doses than possible with independent dose escalation in the four *[hepatic/renal]* dysfunction groups.
* A maximum of 12 patients (1 per participating institution) will be entered into group A (normal *[hepatic/renal]* function). Patients in group A are included in this study to obtain PK data in the same manner as for the patients with liver dysfunction. This group will also be followed for toxicity, but the definitions of recommended dose that are specific to patients with liver dysfunction will not be used.
* In order to define levels of *[hepatic/renal]* impairment at which dose modifications of *[CTEP IND Agent]* are required, data will be combined across *[hepatic/renal]* dysfunction groups to evaluate the association between *[most common/most severe toxicity]*, dose, and *[hepatic]* liver assay level(s) *OR* *[renal]* GFR level(s). The outcome variable, *[most common/most severe toxicity]*, will be modeled as function of dose and *[hepatic]* liver assay *OR* *[renal]* CrCl using multivariate linear regression. Higher order terms of the predictor variables and interactions will be included if there is evidence of non-linear and/or non-additive associations. The regression parameter estimates from this model may then be used to identify the maximum dose which would not adversely impact *[most common/most severe toxicity]*, (*e.g.*, *state specific level such as ANC <1000*) for a patient with a given *[liver/kidney]* function profile.
* Toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 (identified and located on the CTEP website at <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>) and relationship to the study drug; results will be tabulated by liver dysfunction group. All patients who receive any amount of *[Study Agent]* will be evaluable for toxicity, but patients who receive other than the prescribed dose and do not experience a DLT will be considered inevaluable for DLT. Patients who are not evaluable for DLT will be replaced.
* The Child-Pugh Classification and Model for End-Stage Liver Disease of all patients will be collected at baseline and will be correlated to the toxicities, PK and PD data seen with *[CTEP IND Agent]* in an exploratory analysis.
* The PK variables described in Section 9.5 will be tabulated and descriptive statistics calculated for each function group. Geometric means and coefficients of variation will be presented for Cmax and AUC(INF) for each group.

## Endpoints

* + 1. Primary Endpoints

The primary endpoints of this study are as follows:

* Determination of the MTD and DLT of *[CTEP IND Agent]* in groups of patients with varying degrees of *[hepatic/renal]* dysfunction (mild, moderate, severe, and *[renal dialysis]*) in order to provide appropriate dosing recommendations for *[CTEP IND Agent]* in such patients.

*[Hepatic only]* Multivariate linear regression will be used to define cutoffs of baseline bilirubin and/or synthetic (albumin), hepatocellular (ALT, AST) and/or ductal (gamma-GT, alkaline phosphatase) hepatic parameters that predict for *[objective/quantitative measurement of most common/most severe toxicity]* at various dose levels of *[CTEP IND Agent].*

Toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 (identified and located on the CTEP website at <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>). The MTD for each hepatic/renal dysfunction group will be defined based on the toxicities observed during the first cycle *[# days]* of treatment.

* *[Hepatic only]* Determination of the level(s) of liver dysfunction (bilirubin and/or synthetic (albumin), hepatocellular (bilirubin, ALT, AST) and/or ductal (gamma-GT, alkaline phosphatase) parameters at which alterations in the pharmacokinetics of *[CTEP IND Agent]* are observed.
* *[Renal only]* Determination of the level(s) of renal dysfunction parameters at which alterations in the pharmacokinetics of *[CTEP IND Agent]* are observed.
  + 1. Secondary Endpoints
* To document the non-DLTs associated with administration of *[CTEP IND Agent]* in patients with *[hepatic/renal]* dysfunction.
* *[Hepatic only]* A secondary endpoint of this study is to calculate the liver dysfunction scores of each patient at baseline and prior to each cycle according to novel makrers of liver dysfunction and to attempt to correlate these values with the effect of *[CTEP IND Agent]* on the patient’s observed toxicities, plasma PK, and pharmacodynamic parameters.
* *[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.

## 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. Please see the Protocol Submission Worksheet (*[*http://ctep.cancer.gov/forms/docs/psw.docx*](http://ctep.cancer.gov/forms/docs/psw.docx)*)* *for a complete description of ethnic and racial categories and a sample table (which is also provided below).*

*Enter actual estimates, whole numbers only (percentages, fractions, or decimals are not acceptable). Note in some cases, an acceptable response is “Do Not Wish to Provide.”*

**PLANNED ENROLLMENT REPORT**

***Enter actual estimates, whole numbers only (percentages, fractions, or decimals are not acceptable). If your study has a screening and treatment component, both screening and intervention planned accruals should be filled out. If your study only has a screening or treatment component, only the relevant table should be completed.***

| **DOMESTIC PLANNED ENROLLMENT REPORT (SCREENING)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Racial Categories** | **Ethnic Categories** | | | | **Total** |
| **Not Hispanic or Latino** | | **Hispanic or Latino** | |
| **Female** | **Male** | **Female** | **Male** |
| American Indian/ Alaska Native |  |  |  |  |  |
| Asian |  |  |  |  |  |
| Native Hawaiian or Other Pacific Islander |  |  |  |  |  |
| Black or African American |  |  |  |  |  |
| White |  |  |  |  |  |
| More Than One Race |  |  |  |  |  |
| **Total** |  |  |  |  |  |

| **INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT (SCREENING)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Racial Categories** | **Ethnic Categories** | | | | **Total** |
| **Not Hispanic or Latino** | | **Hispanic or Latino** | |
| **Female** | **Male** | **Female** | **Male** |
| American Indian/ Alaska Native |  |  |  |  |  |
| Asian |  |  |  |  |  |
| Native Hawaiian or Other Pacific Islander |  |  |  |  |  |
| Black or African American |  |  |  |  |  |
| White |  |  |  |  |  |
| More Than One Race |  |  |  |  |  |
| **Total** |  |  |  |  |  |

***Enter actual estimates, whole numbers only (percentages, fractions, or decimals are not acceptable).***

| **DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Racial Categories** | **Ethnic Categories** | | | | **Total** |
| **Not Hispanic or Latino** | | **Hispanic or Latino** | |
| **Female** | **Male** | **Female** | **Male** |
| American Indian/ Alaska Native |  |  |  |  |  |
| Asian |  |  |  |  |  |
| Native Hawaiian or Other Pacific Islander |  |  |  |  |  |
| Black or African American |  |  |  |  |  |
| White |  |  |  |  |  |
| More Than One Race |  |  |  |  |  |
| **Total** |  |  |  |  |  |

| **INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT (TREATMENT)** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Racial Categories** | **Ethnic Categories** | | | | **Total** |
| **Not Hispanic or Latino** | | **Hispanic or Latino** | |
| **Female** | **Male** | **Female** | **Male** |
| American Indian/ Alaska Native |  |  |  |  |  |
| Asian |  |  |  |  |  |
| Native Hawaiian or Other Pacific Islander |  |  |  |  |  |
| Black or African American |  |  |  |  |  |
| White |  |  |  |  |  |
| More Than One Race |  |  |  |  |  |
| **Total** |  |  |  |  |  |

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## Stratification Factors

Patients will be stratified according to level of *[hepatic/renal]* dysfunction as described in Section 6.1. Dose escalation and determination of the MTD will be carried out separately for each stratum.

*Please specify any additional 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.*

# ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

## Comprehensive Adverse Events and Potential Risks List (CAEPR) for *[CTEP IND Agent]*

*The Comprehensive Adverse Events and Potential Risks (CAEPR) list will be provided with the LOI approval letter. Please insert the CAEPR here.*

## Adverse Event Characteristics

* **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. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>.
* **For expedited reporting purposes only:**
* AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
* *[Include if protocol-specific expedited reporting exclusions will be made]*Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4.
* **Attribution** of the AE:
  + Definite – The AE *is clearly related* to the study treatment.
  + Probable – The AE *is likely related* to the study treatment.
  + Possible – The AE *may be related* to the study treatment.
  + Unlikely – The AE *is doubtfully related* to the study treatment.
  + Unrelated – The AE *is clearly NOT related* to the study treatment.

## Expedited Adverse Event Reporting

* + 1. CTEP-AERS

*If this study will use Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration, this section can be removed.*

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (<https://ctepcore.nci.nih.gov/ctepaers>). The reporting procedures to be followed are presented in the “NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs” which can be downloaded from the CTEP website (<http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm>). These requirements are briefly outlined in the tables below (Section 10.3.4).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

* + 1. Rave-CTEP-AERS Integration

*If this study will use Rave CTEP-AERS Integration, include this section. Additionally, remove Section 10.3.1 to reflect that AEs will be reported in Medidata Rave. Otherwise, this section should be deleted.*

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AEs) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

* *Include the following (highlighted) paragraphs about pre-treatment AEs only if the study requires reporting of pre-treatment AEs.*
* *Pre-existing medical conditions are not considered adverse events and therefore should not be reported on an Adverse Event form.*

Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form.

Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened event should be reported as a routine AE.

* *Make any necessary updates to Late AE reporting determination for treatment-emergent AEs.*

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 Days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

* The reporting period (course/cycle) is correct, and
* AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (*i.e.*, checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members’ website:

* Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*, and
* Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

* NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at <https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf>.
  + 1. Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

* + 1. Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.**

Death due to progressive disease should be reported as **Grade 5 “Disease progression”**in the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

**Phase 0 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention1, 2**

|  |  |
| --- | --- |
| **FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**  **NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)  An adverse event is considered serious if it results in **ANY** of the following outcomes:   1. Death 2. A life-threatening adverse event 3. An adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5. A congenital anomaly/birth defect. 6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6). | |
| **ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below. | |
| **Grade 1 and 2 Timeframes** | **Grade 3-5 Timeframes** |
| 10 Calendar Days | 24-Hour 5 Calendar Days |
| **Expedited AE reporting timelines are defined as:**   * “24-Hour; 5 Calendar Days” - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.   + “10 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE. | |
| 1Serious adverse events that occur **more than** 30 days after the last administration of investigational agent/intervention require reporting as follows:  Expedited 24-hour notification followed by complete report within 5 calendar days for **ALL** Grade 4 and 5 AEs and Grade 3 AEs with at least a possible attribution.  2For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.  Effective Date: May 5, 2011 | |

**Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention 1, 2**

|  |  |  |
| --- | --- | --- |
| **FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**  **NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)  An adverse event is considered serious if it results in **ANY** of the following outcomes:   1. Death 2. A life-threatening adverse event 3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5. A congenital anomaly/birth defect. 6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). | | |
| **ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below. | | |
| **Hospitalization** | **Grade 1 and Grade 2 Timeframes** | **Grade 3-5**  **Timeframes** |
| Resulting in Hospitalization  ≥ 24 hrs | 10 Calendar Days | 24-Hour 5 Calendar Days |
| Not resulting in Hospitalization  ≥ 24 hrs | Not required |
| **NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.  **Expedited AE reporting timelines are defined as:**   * “24-Hour; 5 Calendar Days” - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. * “10 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE. | | |
| 1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:  **Expedited 24-hour notification followed by complete report within 5 calendar days for:**   * All Grade 3, 4, and Grade 5 AEs   **Expedited 10 calendar day reports for:**   * Grade 2 AEs resulting in hospitalization or prolongation of hospitalization   2For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.  Effective Date: May 5, 2011 | | |

**Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention1, 2**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**  **NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)  An adverse event is considered serious if it results in **ANY** of the following outcomes:   1. Death 2. A life-threatening adverse event 3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5. A congenital anomaly/birth defect. 6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). | | | | |
| **ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below. | | | | |
| **Hospitalization** | **Grade 1 Timeframes** | **Grade 2 Timeframes** | **Grade 3 Timeframes** | **Grade 4 & 5 Timeframes** |
| Resulting in Hospitalization  ≥ 24 hrs | 10 Calendar Days | | | 24-Hour 5 Calendar Days |
| Not resulting in  Hospitalization  ≥ 24 hrs | Not required | | 10 Calendar Days |
| **NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR  **Expedited AE reporting timelines are defined as:**   * “24-Hour; 5 Calendar Days” - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. * “10 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE. | | | | |
| 1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:  **Expedited 24-hour notification followed by complete report within 5 calendar days for:**   * All Grade 4, and Grade 5 AEs   **Expedited 10 calendar day reports for:**   * Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization * Grade 3 adverse events   2For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.  Effective Date: May 5, 2011 | | | | |

* + 1. Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 10.4):

| **CTCAE SOC** | **Adverse Event** | **Grade** | **≥24h Hospitalizationa** |
| --- | --- | --- | --- |
|  |  |  |  |
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|  |  |  |  |

a Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

* *Use CTCAEv5.0 terminology to specify a System Organ Class (SOC) and a pertaining Adverse Event (AE) to be excluded from expedited reporting (“protocol-specific exclusion,” or PSE) via CTEP-AERS. Examples:*
* *For example, instead of “Neuropathy” or “Peripheral neuropathy,” which are not CTCAEv5.0 terms, list each specific CTCAEv5.0 term that applies (“Peripheral motor neuropathy,” “Peripheral sensory neuropathy,”* etc.*) and the pertaining SOC “Nervous system disorders”.* 
  + *Instead of “Myelosuppression”, which is not a CTCAEv5.0 term, list the AE “Anemia” from the SOC “Blood and lymphatic system disorders” and the AEs “Lymphocyte count decreased” and “Neutrophil count decreased”, Platelet count decreased”, and “White blood cell decreased” from the SOC “Investigations”.*
* *Enter grades for all AEs listed in the table.* 
  + *Note: If a specific grade X is listed* ***without a prefix symbol of “≤”****, it is assumed that 1) this specific grade plus all lower grades of that AE are excluded from expedited reporting, and 2) all criteria defining that PSE (*e.g.*, “≥24 h hospitalization”) will apply for ≤ grade X.*
  + *If different exclusion criteria should apply to different grades of the same AE, enter pertaining PSEs in separate rows. For example, if grade 4 diarrhea is a PSE* ***unless*** *it results in “≥24 h hospitalization”, but grades 1-3 are PSEs* ***regardless*** *of whether they result in “≥24 h hospitalization”, grade 4 must be entered in a separate row from grades 1-3.*
* *For the “≥24 h hospitalization” column, enter “Regardless” or “No” depending on which of the following applies:* 
  + *If an AE of a grade X* ***is excluded*** *from expedited reporting* ***regardless of whether*** *it results in ≥24 h hospitalization or ≥24 h prolongation of hospitalization of a patient, enter “****Regardless****”.*
  + *“If an adverse event of a grade X is* ***excluded*** *from expedited reporting via CTEP-AERS only when* ***it DOES NOT*** *result in ≥24 h hospitalization or ≥24 h prolongation of hospitalization, enter “****No****”.*
* *If AEs from the same SOC share the same criteria for exclusion from expedited reporting (Grade and Hospitalization), they may be listed in the same row. However, list all applicable individual CTCAEv5.0 terms.*

## Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

*The following paragraph* ***only*** *applies to trials using* ***Medidata Rave****; other trials may delete****:***

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

## Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient’s partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the “NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs” (at <http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm>) for more details on how to report pregnancy and its outcome to CTEP.

## 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.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

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

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

*Indicate form for reporting in Rave, timeframes, and if loading of the pathology report is required.*

## 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.***

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.

|  | Pre-  Study | Wk  1 | Wk  2 | Wk  3 | Wk  4 | Wk  5 | Wk  6 | Wk  7 | Wk  8 | Wk  9 | Wk  10 | Wk  11 | Wk  12 | Off Studyc |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *[CTEP IND Agent]* |  | A |  |  | A |  |  | A |  |  | A |  |  |  |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Concurrent meds | X | X---------------------------------------------------------------------------------------------X | | | | | | | | | | | |  |
| Physical exam | X | X |  |  | X |  |  | X |  |  | X |  |  | X |
| Vital signs | X | X |  |  | X |  |  | X |  |  | X |  |  | X |
| Height | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Weight | X | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Performance status | X | X |  | X |  | X |  | X |  | X |  | X |  | X |
| CBC w/diff, plts | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serum chemistrya | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PT, APTT, INR | X |  |  |  | X |  |  | X |  |  | X |  |  |  |
| GFR measurement |  | X |  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline serum for renal markers | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Liver Function assessment | X |  |  |  | X |  |  | X |  |  | X |  |  |  |
| EKG (as indicated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event evaluation |  | X---------------------------------------------------------------------------------------------X | | | | | | | | | | | | X |
| Tumor measurements | X | Tumor measurements are repeated every  *[# weeks]*  weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | X |
| Radiologic evaluation | X | Radiologic measurements should be performed every  *[# weeks]*  weeks. | | | | | | | | | | | | X |
| B-HCG | Xb |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PK |  | Xd | Xd |  |  |  |  |  |  |  |  |  |  |  |
| *Other tests, as appropriate* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Other correlative studies [for biomarkers, list as the specimen type collected (e.g. Archival Tissue, Tumor Tissue, Blood in Streck Tubes, Blood in EDTA Tubes, Bone Marrow Aspirate) with each specimen type having its own row]e* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| A: *[CTEP IND Agent]*: Dose as assigned; *administration schedule*  a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], GGT, and sodium. **Include serum urea nitrogen and serum creatinine for patients with renal dysfunction**.  b: Serum pregnancy test (women of childbearing potential).  c: Off-study evaluation.  d: Pharmacokinetic samples taken per schedule in Section 5.8.  e: Note: as applicable use footnotes to provide additional clarifications about timing of biomarker collections. | | | | | | | | | | | | | | |

# 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.*

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every *[# of weeks]* weeks. In addition to a baseline scan, confirmatory scans will also be obtained *[# of weeks]* weeks following initial documentation of an objective response.

*Please use either Section 12.1 or Section 12.2 based on study design. Please note that for studies using immunotherapy, Section 12.2 is recommended as it includes both RECIST version 1.1 and iRECIST criteria.*

## Antitumor Effect – Solid Tumors

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

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

* + 1. Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *[CTEP IND Agent]*.

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 AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

## Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol 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; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution’s data safety monitoring plan.

## Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

* Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, and
* Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

* + Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
  + Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR), and
  + Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
* Refer to <https://ctep.cancer.gov/investigatorResources/default.htm> for registration types and documentation required.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata.  No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed.  Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory.  Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members’ website in the Data Management >Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at [ctsucontact@westat.com](mailto:ctsucontact@westat.com).

*Include the following only if the study will use Transfer of Images and Data (TRIAD); an American College of Radiology’s (ACR) image exchange application, otherwise delete.*

Transfer of Images and Data (TRIAD) is the American College of Radiology’s (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

* Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
* Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the [CTEP](file:///C:/Users/dmanfredi/AppData/Local/Microsoft/Windows/Temporary%20Internet%20Files/Content.Outlook/IRDNJLHZ/NRG-BN001%203%2011%2014.docx#_5.0__REGISTRATION) Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
* TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at <https://triadinstall.acr.org/triadclient/>.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [TRIAD-Support@acr.org](mailto:TRIAD-Support@acr.org) or 1-703-390-9858.

* + 1. Method

*The monitoring method will be determined by CTEP and communicated to you. Please use the appropriate text relating to your assigned monitoring method, and delete any text relating to the unused monitoring methods.*

*For studies assigned for* ***CTMS Comprehensive*** *Monitoring:*

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at <http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11>. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at [CTMSSupport@theradex.com](mailto:CTMSSupport@theradex.com) for additional support with Rave and completion of CRFs.

*For studies assigned for* ***CTMS Routine*** *Monitoring:*

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: <http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11>. On-site audits will be conducted on an 18-36 month basis. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at [CTMSSupport@theradex.com](mailto:CTMSSupport@theradex.com) for additional support with Rave and completion of CRFs.

*For studies assigned* ***DMU Complete*** *monitoring:*

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (<https://ctep.cancer.gov/protocolDevelopment/dmu.htm>).

**Note**: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

*For studies assigned* ***DMU Light*** *monitoring:*

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (<https://ctep.cancer.gov/protocolDevelopment/dmu.htm>).

**Note**: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

*For studies assigned* ***Demography*** *monitoring* ***and*** *enrolling patients via* ***OPEN****:*

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

**Note:** Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

*For studies assigned* ***Demography*** *monitoring* ***and******NOT*** *enrolling patients via* ***OPEN****:*

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative patient demographic data will be submitted weekly to CTEP electronically via the DMU. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (<https://ctep.cancer.gov/protocolDevelopment/dmu.htm>).

**Note:** Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

*For studies assigned for Central Monitoring (CM), keep the following 3 paragraphs and two instructional bullet points:*

Central Monitoring (CM) Review is required for this protocol.  CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients’ charts (*i*.*e*., source data verification).

Sites can upload redacted source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP). This application is available on the CTSU members’ website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form.  Site staff with the CRA or Investigator roles in Rave can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU members’ website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or [ctsucontact@westat.com](mailto:ctsucontact@westat.com)).

* *Include CM requirements determined by the LPO or Lead Academic Organization (LAO) and NCI in this section.*
* *Note to LPO: All LPOs have access to view information related to source document submissions for their associated protocols on the SDP located in the Auditing & Monitoring section of the CTSU website. LPO staff with roles of CM Triage and CM Review on the CTSU roster in RSS can view uploaded source documents to perform triage and review for central monitoring.  LPOs are responsible for completing the OPEN-Rave checklist for the study and submitting it to the CTSU.  Identifying the study as requiring CM on the OPEN-Rave checklist alerts the CTSU to set the Central Monitoring flag in RSS.  LPOs must set up all data points requiring CM Review in Rave prior to submitting the OPEN-Rave checklist to the CTSU.  Once the Central Monitoring flag in RSS is set, the SDP will start pulling data from Rave.*

*For protocols including advanced imaging, please specify ALL requirements, timing, mechanisms, systems, and backups to be used for recording data to CRFs and reporting data to NCI. Include description of local or centralized image review.*

* + 1. Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (<http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm>) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (<http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models>). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial’s lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (<http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm>).

## Data Quality Portal

*Include this section only if the study will use the Data Quality Portal; otherwise, delete.*

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members’ website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website.  Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

*Include the following paragraph only if study is* ***not*** *using the Calendaring functionality in Rave; otherwise, delete.*

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count.

## CTEP Multicenter Guidelines

*The below guidelines must be followed for studies that are* ***not*** *using the CTSU/OPEN rostered model. Suggested text is provided below which can be modified as necessary. If this study uses CTSU/OPEN, or if this study is being performed within a single institution, this section should be marked “N/A” and the text below deleted.*

This protocol complies with the requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Organ Dysfunction Working Group Coordinator) and the procedures for auditing are presented in Appendix D.

The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required. Submit documentation of reportable adverse events to [CTSUprotocol@westat.com](mailto:CTSUprotocol@westat.com) and state in the subject line “Safety Report for *NCI protocol #*” or “Action Letter for *NCI protocol #*”, as appropriate. A brief summary cover page on Coordinating Center letterhead is encouraged. These documents will be posted to the CTSU protocol web page and included in the next CTSU bi-monthly broadcast.

Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the CTSU Regulatory Office as detailed in the Site Registration section of this protocol. The CTSU Regulatory Office will enter and track IRB approval information in the CTSU Regulatory Support System (RSS) where it will be transmitted to CTEP for fulfillment of agent requests.

## Collaborative Agreements Language

*If a study agent is provided by CTEP under a Collaborative Agreement [Cooperative Research and Development Agreement (CRADA), Clinical Trials Agreement (CTA), Agent-CRADA or Clinical Supply Agreement (CSA)] with the Pharmaceutical Company, this section must be included in the protocol. Information on the study agent’s Agreement status will be provided in the approved LOI response. If no Collaborative Agreement applies to the investigational study agent, this section should be marked “N/A” and the text below deleted.*

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator”

(<http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm>) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data”):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (<http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm>). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: [ncicteppubs@mail.nih.gov](mailto:ncicteppubs@mail.nih.gov)

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator’s confidential/ proprietary information.

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

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# APPENDIX A CLASSIFICATION BY LIVER DYSFUNCTION

Child Pugh Classification (CPC) score is calculated from the sum of the points for each CPC criteria:

|  |  |  |
| --- | --- | --- |
| **CPC Classification** | **Level of dysfunction** | **Score** |
| A | Mild | 5-6 |
| B | Moderate | 7-9 |
| C | Severe | ≥10 |

|  |  |  |  |
| --- | --- | --- | --- |
|  | Points | | |
| CPC Criteria | 1 | 2 | 3 |
| **Encephalopathy grade (see table below)** | **0** | **1 or 2** | **3 or 4** |
| **Ascites** | **Absent** | **Asymptomatic** | **Requiring intervention** |
| **Serum bilirubin, mg/dL** | **<2** | **2 to 3** | **>3** |
| **Serum albumin, g/dL** | **>3.5** | **2.8 to 3.5** | **<2.8** |
| **Prothrombin time, sec prolonged** | **<4** | **4 to 6** | **>6** |

|  |  |
| --- | --- |
| Encephalopathy Grade | Definition (EEG required for Gr. 2,3,4) |
| **0** | **Normal consciousness, personality, neurological exam** |
| **1** | **Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting** |
| **2** | **Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG** |
| **3** | **Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves on EEG** |
| **4** | **Unarousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity on EEG** |

CPC should be calculated at baseline and prior to each treatment cycle.

MELD is calculated as follows:

The Maddrey discriminant function is calculated as follows:

**df = [4.6 × (prothrombin time, in seconds)] + (serum total bilirubin, in mg/dL)**

Interpretation of the df values in patients with acute alcoholic hepatitis was that the disease was not severe if df <54, was severe if 55 to 92, and probably lethal if 93 or more and untreated.

The Mayo Survival Model for Primary Biliary Cirrhosis is calculated as follows:

**S(t), survival probability for t years = {S0(t)} exp(R-5.07)**, where

R = 0.871 ln (B) + 2.53 ln (A) + 0.039 (Y) + 0.859 (E) + 2.38 ln (PT).

[S(t) = estimated survival time, R = mortality risk, B=bilirubin, mg/dL; A=albumin, g/dL; Y=age in years; E=edema; PT=prothrombin time, sec]

(Dickson *et al*., 1989)

NOTE: A calculator can be found at:

<https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/natural-history-model-for-primary-biliary-cirrhosis>

The Revised Mayo Natural History Model for Primary Sclerosing Cholangitis is calculated as follows:

**S(t), survival probability for t years = {S0(t)} exp(R-5.07)**, where

R = 0.03 (Y) + 0.54 loge (B) + 0.54 loge (AST) + 1.24 (VB) - 0.84 (A [g/dL]).

[S(t) = estimated survival time, R = mortality risk, B=bilirubin, mg/dL; A=albumin, g/dL; AST= aspartate aminotransferase in U/L; Y=age in years; variceal bleeding as no history (0) or past history (1)]

(Kim *et al*., 2000)

NOTE: A calculator can be found at:

<https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/the-revised-natural-history-model-for-primary-sclerosing-cholangitis/itt-20434725>

# APPENDIX B FORMULA FOR ESTIMATION OF KIDNEY FUNCTION

Renal function levels in clinical trials are commonly described in terms of creatinine clearance (CrCl) calculated using a formula such as Cockcroft-Gault (Cockcroft and Gault, 1976). This formula estimates CrCl based on the serum creatinine concentration in a 24-hour urine collection plus a single measurement of serum creatinine or a single measurement of serum creatinine in addition to demographic data. The drawbacks of the method include the inconvenience of the 24-hour urine collection and its estimation of CrCl rather than glomerular filtration rate (GFR), generally accepted as the best overall index of renal function. Moreover, methods based on creatinine levels in urine overestimate GFR because both secreted and filtered creatinine are measured. The GFR correlates more closely with the renal excretion of many drugs than does CrCl, but the “gold standard” methods for GFR measurement are impractical or unavailable in the clinical setting.

Novel formulae have been developed by the nephrology field to more accurately and precisely estimate GFR. Initially this was the formula developed and validated during the analysis of the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al.*, 1999), followed by (at the time of writing) the CKD-EPI equation (Inker *et al*., 2012), and it is expected that the standard for determining eGFR will keep improving the newer formulae. Therefore, the kidney function of patients enrolled on oncology organ dysfunction trials should be evaluated with the most current standard available at initiation of study.

To simplify the apparent difficulty of the calculations, a “GFR calculator” can be found at <https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr> as well as at other websites.

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

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31-41.

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# APPENDIX C 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 D CTEP MULTICENTER GUIDELINES

*This appendix is for* ***Non-Network*** *trials only. ETCTN trials may delete this appendix.*

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the guidelines below must be followed.

Responsibility of the Protocol Chair

* The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
* The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
* The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
* The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

* Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH.The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
* Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
* The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
* The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
* The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
* Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, *etc.*, available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

* The protocol must include the following minimum information:
* The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
* The Coordinating Center must be designated on the title page.
* Central registration of patients is required. The procedures for registration must be stated in the protocol.
* Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
* Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
* Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

* Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

# APPENDIX E MODEL ELIGIBILITY SCREENING WORKSHEET AND REGISTRATION FORM

**A Phase 1 and Pharmacokinetic Single Agent Study of *Study Agent***  **in Patients**

**with Advanced Malignancies and Varying Degrees of Liver Dysfunction**

**Physician of record: Site Co-Investigator:**

NCI Investigator Number: NCI Investigator Number:

Institution Name: Participating Site (Institution):

NCI Site Code: NCI Site Code:

Address: Address:

Phone: ( ) Phone: ( )

Fax: ( ) Fax: ( )

E-mail: E-mail:

**……*Patient Initials (First, Middle, Last) Patient Date of Birth (mm/dd/yyyy)***

**PATIENT DISEASE**

Primary Disease Site Stage of Disease

Disease Grade Histology

**ELIGIBILITY CHECKLIST**

□ No□ *Yes* 1. Patient has a histologically or cytologically confirmed solid or hematologic malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

□ No □ *Yes* 2. Patient is > 18 years of age.

□ No□ *Yes* 3. Life expectancy is greater than 3 months.

□ No□ *Yes* 4. Patient’s performance status (ECOG scale) is < 2 (Karnofsky > 60%)

□ No□ *Yes* 5. Patient has acceptable marrow and renal function as defined below:

- ANC > 1.5 x 109/L

* platelet count > 100 x 109/L
* glomerular filtration rate (eGFR) >60 mL/min/1.73 m2

□ No□ *Yes* 6. Patient is free of unstable or untreated (non-irradiated) brain metastases.

□ *No* □ Yes 7. Does patient have a history of allergic reactions to compounds of similar chemical or biologic composition to *Study Agent.?*\_

□ *No* □ Yes 8. Does patient have any intercurrent illness including (but not limited to) the following:

* ongoing or active infection
* symptomatic congestive heart failure
* unstable angina pectoris
* cardiac arrhythmia
* psychiatric illness/social situations that would limit compliance with study requirements?

□ *No* □ Yes 9. Is patient pregnant?

□ No□ *Yes* 10. Does patient agree to use adequate means to prevent pregnancy while participating in the study (applies to both male and female patients)?

□ *No* □ Yes 11. Has patient received chemotherapy or radiotherapy within 4 weeks of study entry (6 weeks for nitrosoureas or mitomycin C) and/or has patient not yet recovered from the adverse effects of earlier treatment?

□ *No* □ Yes 12. Has patient undergone major surgery within 14 days prior to registration?

□ *No* □ Yes 13. Has patient received prior therapy with \_\_*Study Agent*\_\_?

□ *No* □ Yes 14. Is patient receiving concurrent therapy with any other investigational agent?

□ *No* □ Yes 15. Is patient receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics of \_*Study Agent*? (Refer to Appendix C.)

□ *No* □ Yes 16. Does patient have active hemolysis or biliary sepsis?

□ *No* □ Yes 17. Is patient HIV positive and receiving combination anti-retroviral therapy?

□ *No* □ Yes 18. *Please insert questions appropriate to agent-specific exclusion criteria.*

**HEPATIC FUNCTION**

Laboratory upper limit of normal for:

Albumin:

SGOT/AST:

SGPT/ALT:

Total bilirubin:

Alkaline phosphatase:

Patient values for:

Total bilirubin raw value\_\_\_\_\_\_\_ □ < ULN□ >1.0-1.5× ULN□ >1.5× – 3× ULN□ >3× ULN

Date measured: / / (mm/dd/yyyy) (Second measurement – for patients with biliary shunt / / )

(mm/dd/yyyy)

SGOT/AST raw value\_\_\_\_\_\_\_ □ < ULN□ > ULN

Date measured: / / (mm/dd/yyyy) (Second measurement – for patients with biliary shunt / / )

(mm/dd/yyyy)

SGOT/AST raw value\_\_\_\_\_\_\_ □ < ULN□ > ULN

Date measured: / / (mm/dd/yyyy) (Second measurement – for patients with biliary shunt / / )

(mm/dd/yyyy)

Prothrombin time \_\_\_\_\_ value; prolonged by \_\_\_\_\_\_ value

Date measured: / / (mm/dd/yyyy)

International normalized ratio for prothrombin time \_\_\_\_\_ value

Date measured: / / (mm/dd/yyyy)

Encephalopathy Grade \_\_\_\_\_ value

Date measured: / / (mm/dd/yyyy)

Edema □ present□ absent

Date measured: / / (mm/dd/yyyy)

Ascites □Absent□ Asymptomatic□ Requiring intervention

Date measured: / / (mm/dd/yyyy)

Variceal bleeding □ no history□ past history

Date measured: / / (mm/dd/yyyy)

Encephalopathy Grade \_\_\_\_\_ value

Date measured: / / (mm/dd/yyyy)

Albumin \_\_\_\_\_ value

Date measured: / / (mm/dd/yyyy)

Serum Creatinine \_\_\_\_\_ value

Date measured: / / (mm/dd/yyyy)

Age (current) \_\_\_\_\_ value

Date measured: / / (mm/dd/yyyy)

**COMMENTS:**

**ELIGIBILITY**: □ Patient satisfies all eligibility criteria.

□ Patient is not formally eligible, but may be admitted to the study because (state reason)\*:

\* **Coordinator must document and date exceptions to eligibility in the record.**

**A Phase 1 and Pharmacokinetic Single Agent Study of *Study Agent***  **in Patients**

**with Advanced Malignancies and Varying Degrees of Liver Dysfunction**

CTEP-assigned Protocol Number Coordinating Center (Local) Protocol Number

Coordinating Center Name Coordinating Center Code

Participating Institution Name Participating Institution Code

Patient Study ID, Coordinating Center Patient Study ID, Participating Institution

Patient Medical Record Number

Physician of Record

**Protocol Administration**

IRB/REB Approval Date Person Completing Form:

MM DD YYYY Last Name

Date Informed Consent Signed First Name

MM DD YYYY Phone (\_\_\_\_)

Projected Start Date of Treatment Fax (\_\_\_\_)

MM DD YYYY E-mail

Date of Registration

MM DD YYYY

**Patient Demographics / Pre-Treatment Characteristics**

Patient Name, Last First Middle

*(initials acceptable) (initials acceptable)* *(initials acceptable)*

Patient Birth Date Patient Gender 🞎 *Male* 🞎 *Female*

MM DD YYYY

Patient Race/Ethnicity 🞎 *White* 🞎 *Black or African American*

***(check all that apply)***🞎 *Native Hawaiian or Other Pacific Islander* 🞎 *Asian*

🞎 *American Indian or Alaska Native* 🞎 *Unknown*

Patient Ethnicity 🞎 *Hispanic or Latino*

***(check one)***🞎 *Non-Hispanic*

🞎 *Unknown*

Patient Social Security Number *(USA only)*

Patient’s ZIP Code *(USA)* Country of Residence *(if not USA)*

Patient Height (cm) Patient Weight (kg) Body Surface Area (m2)

Performance Status ***(check one)*** Method of Payment ***(check one)*** *(U.S. only)*

🞎 *0 = Fully active, able to carry on all pre-disease* 🞎 *Private* 🞎  *Military Sponsored*

*performance without restriction (Karnofsky 90 - 100)* 🞎 *Medicare*  *(including CHAMPUS or TRICARE)*

🞎 *1 = Restricted in physically strenuous activity but* 🞎 *Medicare/Private* 🞎  *Veterans Sponsored*

*ambulatory (K 70 - 80)*

🞎 *2 = Ambulatory and capable of all self care but* 🞎 *Medicaid* 🞎  *Self pay (no insurance)*

*unable to carry out any work activities (K 50 - 60)* 🞎 *Medicaid &* 🞎 *No means of payment*

*Medicare* *(no insurance)*

🞎 *3 = Capable of only limited self care, confined to bed or* 🞎 *Military or Veterans* 🞎 *Other*

*chair more than 50% of waking hours (K 30 - 40)* *Sponsored NOS* 🞎  *Unknown*

🞎 *4 = Completely disabled (K 10 – 20)*

Date Signed Informed Consent Obtained:

MM DD YYYY

**Certification of Eligibility**   **Protocol Design**

Hepatic Dysfunction Group (Cohort)

Dose Level Assignment

*(State exact dose in units, e.g., mg/m2, mcg/kg, etc.)*

In the opinion of the investigator  
is the patient eligible?

🞎 *Yes* 🞎 *No*

*(if No, the patient should not be registered)*

**Initial Patient Consent for Specimen Use**

Patient’s Initial Consent given for specimen use for research 🞎 *Yes* 🞎 *No*

on the patient's cancer?

Patient’s Initial Consent given for specimen use for research 🞎 *Yes* 🞎 *No*

unrelated to the patient's cancer?

Patient’s Initial Consent given for further contact regarding specimen? 🞎 *Yes* 🞎 *No*

Date of Consent for Specimen Use

MM DD YYYY

**A Phase 1 and Pharmacokinetic Single Agent Study of *Study Agent***  **in Patients**

**with Advanced Malignancies and Varying Degrees of Renal Dysfunction**

**Physician of record: Site Co-Investigator:**

NCI Investigator Number: NCI Investigator Number:

Institution Name: Participating Site (Institution):

NCI Site Code: NCI Site Code:

Address: Address:

Phone: ( ) Phone: ( )

Fax: ( ) Fax: ( )

E-mail: E-mail:

***Patient Initials (First, Middle, Last) Patient Date of Birth (mm/dd/yyyy)***

**PATIENT DISEASE**

Primary Disease Site Stage of Disease

Disease Grade Histology

**ELIGIBILITY CHECKLIST**

🞎 No🞎 *Yes* 1. Patient has a histologically or cytologically confirmed solid or hematologic malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

🞎 No🞎 *Yes* 2. Patient is > 18 years of age.

🞎 No🞎 *Yes* 3. Life expectancy is greater than 3 months.

🞎 No🞎 *Yes* 4. Patient’s performance status (ECOG scale) is < 2 (Karnofsky > 60%)

🞎 No🞎 *Yes* 5. Patient has acceptable marrow and renal function as defined below:

- ANC > 1.5 x 109/L

* platelet count > 100 x 109/L
* total bilirubin within normal institutional limits
* AST (SGOT)/ALT (SGPT) <3 X institutional upper limit of normal

🞎 No🞎 *Yes* 6. Patient is free of unstable or untreated (non-irradiated) brain metastases.

🞎 *No* 🞎 Yes 7. Does patient have a history of allergic reactions to compounds of similar chemical or biologic composition to *Study Agent?*\_

🞎 *No* 🞎 Yes 8. Does patient have any intercurrent illness including (but not limited to) the following:

* ongoing or active infection
* symptomatic congestive heart failure
* unstable angina pectoris
* cardiac arrhythmia
* psychiatric illness/social situations that would limit compliance with study requirements?

🞎 *No* 🞎 Yes 9. Is patient pregnant?

🞎 No🞎 *Yes* 10. Does patient agree to use adequate means to prevent pregnancy while participating in the study (applies to both male and female patients)?

🞎 *No* 🞎 Yes 11. Has patient received chemotherapy or radiotherapy within 4 weeks of study entry (6 weeks for nitrosoureas or mitomycin C) and/or has patient not yet recovered from the adverse effects of earlier treatment?

🞎 *No* 🞎 Yes 12. Has patient undergone major surgery within 14 days prior to registration?

🞎 *No* 🞎 Yes 13. Has patient received prior therapy with \_\_*Study Agent*\_\_?

🞎 *No* 🞎 Yes 14. Is patient receiving concurrent therapy with any other investigational agent?

🞎 *No* 🞎 Yes 15. Is patient receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics of \_*Study Agent*\_? (Refer to Appendix C.)

🞎 *No* 🞎 Yes 16. Does patient have active hemolysis?

🞎 *No* 🞎 Yes 17. Is patient HIV positive and receiving combination anti-retroviral therapy?

🞎 *No* 🞎 Yes 18. *Please insert questions appropriate to agent-specific exclusion criteria.*

**RENAL FUNCTION**

Plasma creatinine mg/dL Creatinine clearance mL/min

(CrCl)

/ /

/ /

Date measured: Date measured:

(mm/dd/yyyy) (mm/dd/yyyy)

Calculated BSA-indexed eGFR mL/min/1.73 m2 **(VALUE USED FOR STRATIFICATION)**

(using CKD-EPI formula)

Serum albumin g/dL Serum urea nitrogen mg/dL

/ /

/ /

Date measured Date measured:

(mm/dd/yyyy) (mm/dd/yyyy)

**COMMENTS:**

**ELIGIBILITY:** 🞎 Patient satisfies all eligibility criteria.

🞎 Patient is not formally eligible, but may be admitted to the study because (state reason)\*:

\* **Coordinator must document and date exceptions to eligibility in the record.**

**A Phase 1 and Pharmacokinetic Single Agent Study of *Study Agent***  **in Patients**

**with Advanced Malignancies and Varying Degrees of Renal Dysfunction**

CTEP-assigned Protocol Number Coordinating Center (Local) Protocol Number

Coordinating Center Name Coordinating Center Code

Participating Institution Name Participating Institution Code

Patient Study ID, Coordinating Center Patient Study ID, Participating Institution

Patient Medical Record Number

Physician of Record

**Protocol Administration**

IRB/REB Approval Date Person Completing Form:

MM DD YYYY Last Name

Date Informed Consent Signed First Name

MM DD YYYY Phone (\_\_\_\_)

Projected Start Date of Treatment Fax (\_\_\_\_)

MM DD YYYY E-mail

Date of Registration

MM DD YYYY

**Patient Demographics / Pre-Treatment Characteristics**

Patient Name, Last First Middle

*(initials acceptable) (initials acceptable)* *(initials acceptable)*

Patient Birth Date Patient Gender 🞎 *Male* 🞎 *Female*

MM DD YYYY

Patient Race/Ethnicity 🞎 *White* 🞎 *Black or African American*

***(check all that apply)***🞎 *Native Hawaiian or Other Pacific Islander* 🞎 *Asian*

🞎 *American Indian or Alaska Native* 🞎 *Unknown*

Patient Ethnicity 🞎 *Hispanic or Latino*

***(check one)***🞎 *Non-Hispanic*

🞎 *Unknown*

Patient Social Security Number *(USA only)*

Patient’s ZIP Code *(USA)* Country of Residence *(if not USA)*

Patient Height (cm) Patient Weight (kg) Body Surface Area (m2)

Performance Status ***(check one)*** Method of Payment ***(check one)*** *(U.S. only)*

🞎 *0 = Fully active, able to carry on all pre-disease performance* 🞎 *Private* 🞎  *Military Sponsored*

*without restriction (Karnofsky 90 - 100)* 🞎 *Medicare* *(including CHAMPUS or TRICARE)*

🞎 *1 = Restricted in physically strenuous activity* 🞎 *Medicare/* 🞎  *Veterans Sponsored*

*but ambulatory (K 70 - 80) Private*

🞎 *2 = Ambulatory and capable of all selfcare but* 🞎 *Medicaid* 🞎  *Self pay (no insurance)*

*unable to carry out any work activities (K 50 - 60)* 🞎 *Medicaid &* 🞎 *No means of payment*

*Medicare (no insurance)*

🞎 *3 = Capable of only limited selfcare, confined to bed or* 🞎 *Military or* 🞎 *Other*

*chair more than 50% of waking hours (K 30 - 40)* *Veterans* 🞎  *Unknown*

🞎 *4 = Completely disabled (K 10 – 20) Sponsored NOS*

Date Signed Informed Consent Obtained:

MM DD YYYY

**Certification of Eligibility**   **Protocol Design**

Renal Dysfunction Group (Cohort)

Dose Level Assignment

*(State exact dose in units, e.g., mg/m2, mcg/kg, etc.)*

In the opinion of the investigator  
is the patient eligible?

🞎 *Yes* 🞎 *No*

*(if No, the patient should not be registered)*

**Initial Patient Consent for Specimen Use**

Patient’s Initial Consent given for specimen use for research on the patient's cancer? 🞎 *Yes* 🞎 *No*

Patient’s Initial Consent given for specimen use for research unrelated to the patient's cancer? 🞎 *Yes* 🞎 *No*

Patient’s Initial Consent given for further contact regarding specimen? 🞎 *Yes* 🞎 *No*

Date of Consent for Specimen Use

MM DD YYYY

# APPENDIX F PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

***Instructions for Patient drug interactions handout and wallet card Template***

*Patient Drug Interactions Handout and Wallet Card is a requirement that must meet CTEP Policies & Procedures for non-marketed investigational agents. The instructions below specify which template to use. Please note the drug interactions handout and wallet card require IRB approval before distribution to patients.*

***Instructions to authors:*** *Refer to the table below to determine which template (Template A or Template B) you should use and fill out the appropriate information as instructed by the template. Use or delete sections below as appropriate.****Only edit the fillable text fields – do not alter any text outside of the fillable fields. The bracketed instruction text will disappear once you begin typing.***

* 1. ***Template A: Patient Drug Interactions Handout and a Patient Drug Interactions Wallet Card*** 
     1. *To be given at the time of enrollment and when updated.*
     2. *A protocol that has more than one non-marketed investigational agent with PK interactions will have a drug interactions handout and drug interactions wallet card for each agent.*
     3. *Assign a letter or a Roman numeral to the Appendix.*
     4. *A convenient wallet-sized information card for the patient to cut out and retain at all times.*
     5. ***Suggested texts to complete the templates are on the next page.***
     6. ***Use the fillable template and enter information in the fillable fields****.*
  2. ***Template B: Patient Clinical Trial Wallet Card only***
     1. *To be given to the patient at the time of enrollment.*
     2. *A convenient wallet-sized information card for the patient to cut out and retain at all times.*
     3. *Assign a letter or a Roman numeral to the Appendix.*
     4. ***Suggested texts to complete the template are on the next page****.*
     5. ***Use the fillable template and enter information in the fillable fields.***

*When the Patient Drug Interactions Handout and Wallet Card is required and who is responsible for the authorship is summarized in table below:*

| *Clinical Trial Sponsor* | *Is Agent Marketed?*  *Yes (Y)/ No (N)* | *Does Agent Have*  *Drug-Interactions Potential? (Y/N)* | *Is a Patient Drug Interactions Handout and Wallet Card required? (Y/N)* | *Who is responsible for authorship?* | *Template Required* |
| --- | --- | --- | --- | --- | --- |
| *CTEP-IND* | *N* | *Y* | *Y* | *PMB* | *A* |
| *CTEP-IND* | *N* | *N* | *N* | *N/A* | *B* |
| *CTEP-IND* | *Y* | *Y or N* | *N* | *N/A* | *B* |
| *Non-CTEP IND* | *N* | *Y* | *Y* | *Lead Organization* | *A* |
| *Non-CTEP IND* | *N* | *N* | *N* | *N/A* | *B* |
| *Non-CTEP IND* | *Y* | *Y or N* | *N* | *N/A* | *B* |

***Template A****:* **Patient drug interactions handout and patient drug interactions wallet card**

**APPENDIX      : PATIENT DRUG Interactions handout and wallet card**

**Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Patient Name:** |  | **Diagnosis:** |  | **Trial #:** |  |
| **Study Doctor:** |  | **Study Doctor Phone #:** |  | **Study Drug(s):** |  |

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

**These are the things that your healthcare providers need to know:**

*[Insert study drug]* interacts with [certain specific enzyme(s) in your liver or other tissueslike the gut],[certain transport proteins that help move drugs in and out of cell]*,* [the heart’s electrical activity (QTc prolongation)]*.*

|  |  |
| --- | --- |
|  | **Explanation** |
| CYP isoenzymes | The enzyme(s) in question is/are *[enter name of CYP isoenzyme(s)]*. [Insert brief, easy explanation of the nature of the interaction, i.e., for substrates: “[insert study drug name] is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.”] |
| Protein transporters | The protein(s) in question is/are *[enter name of transporter(s)]*. [Insert brief, easy explanation of the nature of the interaction, i.e., for substrates: “[insert study drug name] is moved in and out of cells/organs by this transport protein.”] |
| Heart’s electrical activities | The heart’s electrical activity may be affected by [Insert study drug]*.* The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation. |

**These are the things that you need to know:**

The study drug [Insert study drug],may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e*.*g*. St. John’s Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered *[“strong inducers/inhibitors or substrates] of [name(s) of CYP isoenzyme(s)], [transport protein(s), or any medicine associated with greater risk for having QTc prolongation.”]*

* Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

* + [Add other specific medications here, if necessary. Examples include acid suppressing drugs, NSAIDS, St. John’s Wort.]
* Make sure your doctor knows to avoid certain prescription medications.

* + [Add other specific medications here, if necessary. Examples include acid suppressing drugs, anticoagulants, NSAIDS.]
* Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Version *mmm/yyyy*

(Next page: Patient Drug Interaction Wallet Card)

***Template A:*** **Patient Drug Interaction Wallet Card**

****

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| **EMERGENCY INFORMATION** |  | **dRUG INTERACTIONS** | |
| **Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.** | Tell your doctors **before** you **start** or **stop** any medicines.  **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!** | **Carry this card with you at all times**  [insert study drug]interacts with [a specific enzyme in your liver or other tissues like the gut, transport proteins that help move drugs in and out of cells, the heart’s electrical activity,] and must be used very carefully with other medicines. | |
| **Patient Name:** | **Use caution and avoid the following drugs if possible:**  [List specific medications here. Examples: OTC drugs, herbal supplements, vitamins, acid suppressing drugs, anticoagulants, NSAIDs, digoxin.] | Your healthcare providers should be aware of any medicines that are [strong inducers/inhibitors/substrates of [insert CYP isoenzymes], interact with [insert transport proteins], or affect your heart’s electrical activity]. | |
| **Diagnosis:** |
| **Study Doctor:** |
| **Study Doctor Phone #:** |
| **NCI Trial #:** | **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. | |
| **Study Drug(S):** |
|  | Versionmmm/yyyy |
| **For more information:** 1-800-4-CANCER | **For more information:** 1-800-4-CANCER | **For more information:** 1-800-4-CANCER | **For more information:** 1-800-4-CANCER |
| cancer.gov | clinicaltrials.gov | cancer.gov | clinicaltrials.gov | cancer.gov | clinicaltrials.gov | cancer.gov | clinicaltrials.gov |

|  |  |  |  |
| --- | --- | --- | --- |
| *Fold at dotted lines*: |  |  |  |

***Template B:* Patient Clinical Trial wallet card**

**Appendix** [enter letter/number]**: Patient clinical trial wallet card**

****

|  |
| --- |
|  |
| **cliniCal trial wallet card** |
| **Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.** |
| **Patient Name:** |
| **Diagnosis:** |
| **Study Doctor:** |
| **Study Doctor Phone #:** |
| **NCI Trial #:** |
| **Study Drug(S):** |
|
| **For more information:** 1-800-4-CANCER |
| cancer.gov | clinicaltrials.gov |

# APPENDIX G PRE-BIOPSY ASSESSMENT

A pre-biopsy lesion assessment can increase trial safety and efficiency. By agreement between all investigators, an attempt at biopsy will be made if the clinical trial team determines that a biopsy poses minimal relative risk, provides potential clinical gain to the participant, and will likely yield sufficient tissue for analysis.

Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system. Additional information can be found in the Investigational Radiology SOP available at:

[https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN\_IR\_Research\_Biopsy\_SOP.pdf](https://na01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fctep.cancer.gov%2FinitiativesPrograms%2Fdocs%2FETCTN_IR_Research_Biopsy_SOP.pdf&data=01%7C01%7Cjsager%40tech-res.com%7Cf468cc828dcf4b51979c08d698d7e103%7C806430642666421e89e796efca3d7489%7C0&sdata=Fbt0UmITgBEKLuX%2Fkcvndg0XjGz42xvk1w5L53FPuXw%3D&reserved=0).

**Individual Patient Pre-Biopsy Assessment.** IR co-investigators are encouraged to apply this pre-biopsy scoring and correlation system to assist in the determination of biopsy appropriateness.

* + - * + IR co-investigators assign a subjective score of 1-3 based on likelihood of success due to lesion characteristics.

1. Biopsy should not be done

1. Due to safety concerns
2. Due to lack of suitable lesion for biopsy

2. Uncertainty about success

1. Due to access path to lesion
2. Due to lesion characteristics

3. Likely successful

* + - * + Lesion characteristics to be considered
* Size (small) (<2 cm)
* Location/path to lesion
* Morphologic features (necrosis, sub-solid, sclerosis, ill-defined/infiltrative)
* PET (+/-), avidity
* Organ/site (sclerotic bone is low yield; fine needle aspiration to be used)

# APPENDIX H INTEGRAL BIOMARKERS

*Investigational laboratory assays employed as integral biomarkers should be described here.*  ***ETCTN***  *trials may use and insert here the “Study Checklist for Early Phase Trials with CTEP-Supported Biomarker Assays” for ETCTN studies (this form can be found at* <http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm>*).*

*If the protocol includes any* ***integral*** *biomarker studies using* in situ *hybridization (ISH),immunohistochemistry (IHC), and/or DNA-based mutation assays, you may fill out the appropriate template (found at* <http://ctep.cancer.gov/protocolDevelopment/ancillary_correlatives.htm>*) and attach to this protocol submission as separate Appendices.*

*If the laboratory or laboratories performing the studies has an alternatively-formatted document that supplies the same level of information regarding validation, materials and methods,* etc*., it may be used instead of the templates.*

# APPENDIX I TISSUE BIOPSY VERIFICATION

*Edit the grey-highlighted text for Tissue Type and Time Point as appropriate for this study and then remove this instruction and the grey highlighting.*

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the

EET Biobank.

**If the *corresponding* pathology report is not available for the biopsy, then a copy of the radiology report or operative report from the biopsy procedure and the diagnostic pathology report must be sent to the EET Biobank. A completed copy of this appendix (i.e., Tissue Biopsy Verification) must also be submitted to the EET Biobank.**

**Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.**

Please have the Clinician\* responsible for signing out this patient’s case complete the following:

**ETCTN Universal Patient ID:**

**ETCTN Patient Study ID:**

**Date of Procedure (mm/dd/yyyy):**

**Tissue Type (circle one): Primary Metastatic**

**Time point (circle one): Timepoint1 TimePoint2 Timepoint3**

**Site Tissue Taken From:**

**Diagnosis:**

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient’s care.

Clinician Signature Date

Clinician Printed Name

\*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient’s care.

Version: 1

# APPENDIX J NCLN PHARMACODYNAMICS LABORATORY FROZEN BIOPSY COLLECTION PROCEDURE

*If your study is using the NCLN Pharmacodynamics Laboratory for an assay requiring a frozen needle tumor biopsy, include this Appendix.* *Customize the protocol text for your study and reference this appendix in the body of the protocol.*

Graphical user interface, text, application

Description automatically generated

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Title: | Tumor Frozen Needle Biopsy Specimen Collection, Handling and Shipment to EET Biobank | | | | Page 2 of 13 |
| Doc. #: | SOP340567 | Revision: | - | Effective Date: | 10/08/2021 |

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|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Title: | Tumor Frozen Needle Biopsy Specimen Collection, Handling and Shipment to EET Biobank | | | | Page 3 of 13 |
| Doc. #: | SOP340567 | Revision: | - | Effective Date: | 10/08/2021 |

**1.0 PURPOSE**

Standardize the method for collecting, handling, and shipping frozen needle tumor biopsies to EET Biobank to enable measurement of pharmacodynamic (PD) markers following treatment with anti-cancer agents.

**2.0 SCOPE**

This procedure applies to all personnel involved in the collection and handling of frozen needle tumor biopsies for use in PD marker assays during clinical trials. The goal of this SOP and associated training is to ensure consistency in tumor needle biopsy collection and handling between clinical sites..

**3.0 ABBREVIATIONS**

|  |  |  |
| --- | --- | --- |
| DCTD | = | Division of Cancer Treatment and Diagnosis |
| EET Biobank | = | NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank, also referred to as the Nationwide Biorepository or ETCTN Biorepository |
| FNLCR | = | Frederick National Laboratory for Cancer Research |
| ID | = | Identification / Identifier |
| IQC | = | Internal Quality Control |
| LHTP | = | Laboratory of Human Toxicology and Pharmacology |
| PADIS | = | Pharmacodynamics Assay Development & Implementation Section |
| PD | = | Pharmacodynamic |
| SOP | = | Standard Operating Procedure |

**4.0 INTRODUCTION**

Specimen handling, shipping, and storage procedures (pre-analytical variables) can have a significant impact on the reliability of biomarker measurements in the laboratory. Following detailed steps for sample collection and handling procedures and recording any deviations from this procedure allow retrospective identification of artifactual changes in biomarker readout and increases the reliability of the data and validity of the analytical results.

* 1. **ROLES AND RESPONSIBILITIES**

Laboratory Director/Supervisor: The Laboratory Director/Supervisor directs laboratory operations, supervises technical personnel and reporting of findings, and is responsible for the proper performance of all laboratory procedures. Oversees the personnel who follow the SOPs in the laboratory and is responsible for ensuring the personnel are certified and have sufficient experience to handle clinical samples.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Title: | Tumor Frozen Needle Biopsy Specimen Collection, Handling and Shipment to EET Biobank | | | | Page 4 of 13 |
| Doc. #: | SOP340567 | Revision: | - | Effective Date: | 10/08/2021 |

Certified Assay Operator and/or PK/PD Support Lab Personnel: An assay operator and/or PK/PD Support Lab personnel may be a Laboratory Technician/Technologist, Research Associate, or Laboratory Scientist who has been trained by DCTD personnel on this SOP. Working under the guidance of the Laboratory Director/Supervisor, this person performs laboratory procedures and examinations in accordance with the current SOP(s), as well as any other procedures conducted by a laboratory, including maintaining equipment and records and performing quality assurance activities related to performance.

* 1. It is the responsibility of the Laboratory Director/Supervisor to ensure that all personnel have documented training and qualification on this SOP prior to the actual handling and processing of samples from clinical trial patients. The Laboratory Director/Supervisor is responsible for ensuring the assay operator running the SOP has sufficient experience to handle and analyze clinical samples. To become proficient with this SOP, sites are highly encouraged to reach out to [NCI\_PD\_Support@mail.nih.gov](mailto:NCI_PD_Support@mail.nih.gov) for additional training materials.
  2. It is the responsibility of the assay operator to confirm scheduled specimen collection time points, pre-print all labels, request access to **NCI Medidata Rave** (ETCTN Specimen Tracking System), check documentation for accuracy, request sample shipping kits from the EET Biobank and verify that the required collection tubes, supplies, and equipment are available for successful collection and handling of biopsy samples.
  3. It is the responsibility of the assay operator to conduct the specimen collection and handling procedures following this SOP and complete the required tasks and associated documentation. The Biopsy Collection Record ([Appendix 1](#_bookmark8)) must be completed for each patient sample collection and filed with the study patient’s other records.
  4. The responsible personnel are to check the DCTD Biomarkers Web site (<http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm>) to verify that the latest SOP version is being followed.
  5. **MATERIALS AND EQUIPMENT REQUIRED**
  6. Stopwatch, total time in minutes and seconds required
  7. 1.5-mL Sarstedt o-ring screw cap, conical bottomed tubes (Sarstedt, Cat#: 72.703.416)
  8. Disposable, fine-tipped tweezers (e.g., VWR, Cat#: 83009-010). Tweezer tips need to easily fit to the bottom of a 1.5-mL Sarstedt tube
  9. Printable microcentrifuge tube labels or BSI labeling system
  10. 81-place freezer boxes (e.g., Fisher Scientific, Cat#: 12-565-182)
  11. Thermoflask cooler or polystyrene foam container
  12. Ice bucket
  13. Liquid nitrogen or dry ice/ethanol bath
  14. -80°C freezer (or colder)
  15. Specimen shipping kit from EET Biobank

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* 1. **OPERATING PROCEDURES**
  2. This SOP uses **NCI Medidata Rave** for sample tracking, please review the following training videos for **NCI Medidata Rave** before you start:
     1. General RAVE training: <https://www.youtube.com/watch?app=desktop&v=ZRX0lSqs5zo>
     2. Label Printing training: <https://www.youtube.com/watch?app=desktop&v=9_Q6_k-KHHs>
  3. Sample Shipping Kits

Sample shipping kits should be requested prior to enrolling the first biopsy patient from EET Biobank by emailing [BPCBank@nationwidechildrens.org](mailto:BPCBank@nationwidechildrens.org). For current customers, the kits can be requested through the EET Biobank (kit management system: <https://kits.bpc-apps.nchri.org/Auth/Login?ReturnUrl=%2f>). Please allow 5-7 business days for kit shipment.

* 1. Labels
     1. Prepare enough pre-printed specimen labels in **NCI Medidata Rave** by following steps 7.3.1.1- 7.3.1.5:
        1. Log into **NCI Medidata Rave** and go to **Enrollment** folder and confirm the **Histology and Disease** form is complete.
        2. Go to **All Specimens** folder.
        3. Complete the **Specimen Consent** form.
        4. Complete the **Specimen Tracking Enrollment** form for each specimen.
        5. Complete the **Print Labels** form. Labels will be sent to user’s email address. For tissue specimens, apply appropriately coded label to each pass of the biopsy (see below).

Note: Five labels will be printed by default when you enter “**1**” in the “**How many labels are needed**” field. The first four will be designated with A, B, C and D to represent different passes of the biopsy procedure. Please use those accurately to label the specimens; pass A should be for the first pass, B for the second, etc. The fifth label will have no pass designation and can be used on reports to be uploaded into RAVE. See an example of pre-printed label for frozen tissue biopsy below.

Text

Description automatically generated

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* 1. Tumor Needle Biopsy Collection and Handling
     1. The research nurse is to notify the laboratory of scheduled PD sample collections, preferably giving at least 24 hours of notice. Arrive at the biopsy collection site early enough to allow sufficient time to set up laboratory supplies, collect relevant clinical information, and ensure rapid transport of frozen specimens from the procedure area to the laboratory, where they will be placed into storage at -80ºC (or colder).
     2. Prior to biopsy, the lesion should be assessed as to whether or not the biopsy should be performed and yield a successful outcome. Fill out the **Pre-Biopsy Lesion Score** form in **NCI Medidata Rave** using inputs from interventional radiologists and/or oncologists.
     3. Bring all necessary lab supplies to the biopsy collection site, including: disposable tweezers, a minimum of four 1.5-mL Sarstedt tubes pre-cooled on liquid nitrogen or dry ice/ethanol in an insulated bucket (Sarstedt tubes will be provided in the sample shipping kit from EET Biobank; please use one tube for each whole biopsy core), the label with no pass designation to give to the research nurse for the patient record, and a printout of [Appendix 1](#_bookmark8).

**Note**: Pre-chill additional 1.5-mL Sarstedt tubes for specimen collection in case the interventional radiologist collects additional passes, or if one of the tubes is compromised prior to collection.

* + 1. The total time elapsed between biopsy collection and placement into the pre- chilled tube is of **key importance** to biomarker analysis; this time should be documented in **NCI Medidata Rave** for each biopsy pass. **It is important to note that all biopsies should be frozen within 2 minutes of collection.** The interventional radiologist will eject the biopsy onto a sterile slide (for optimal analyte recovery the slide should be pre-chilled). Start a stopwatch at this point (or note the time in [Appendix 1](#_bookmark8)) and immediately walk the slide to the sample preparation table for transfer to the pre-chilled Sarstedt tube.
    2. Immediately snap freeze the biopsy by placing the tube in liquid nitrogen or a dry ice/ethanol bath (stop the stopwatch at this point). **Note:** DO NOT let the tubes tip over in the liquid nitrogen or dry ice/ethanol bath.
    3. Calculate the total time elapsed from biopsy collection to biopsy freezing and record the total number of **minutes and seconds** ([Appendix 1](#_bookmark8)).
    4. Note the specific needle type used and location of each biopsy pass collected (*e.g.*, spleen, large left upper quadrant splenic mass) ([Appendix 1](#_bookmark8)).
    5. Note the protocol biopsy timepoint in [Appendix 1](#_bookmark8).
    6. Return to the sample processing laboratory and transfer the frozen biopsy specimen(s) to -80°C (or colder) for storage until shipment to the EET Biobank.
    7. After biopsy collection, complete sample tracking documentation in **NCI Medidata Rave** according to notes recorded in [Appendix 1](#_bookmark8).

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* + 1. Fill out **Biopsy Report** form in the **All Specimen** folder.

Note: It is very important to record the site of the biopsy to the **Tumor Site Location** field as shown below.

Graphical user interface, text, application

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* + 1. Complete the **Specimen Transmittal** form in the All Specimen folder.

**Note:** It is important to fill out the time from collection to frozen for each pass in the **Specimen Transmittal** form by following the instructions below.

Pass A time will be recorded in the appropriate fields as shown below:

Graphical user interface, text, application

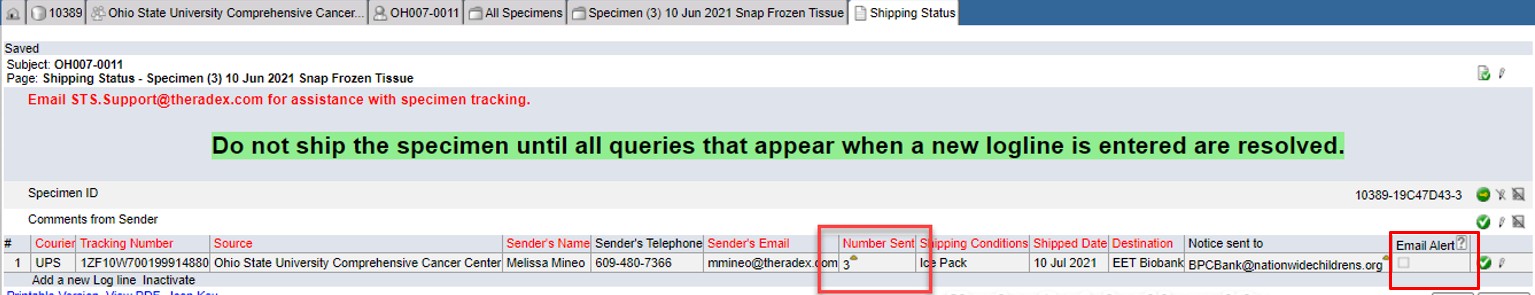
Description automatically generated

Times elapsed for passes B, C and D will be recorded in the **Comment** field near the bottom of the Specimen Transmittal form as shown below. Biopsy passes not collected will also be recorded in the **Comment** field as shown below.

Graphical user interface, text, application, Word

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* 1. **SHIP TO EET BIOBANK**
  2. When specimens are ready to be shipped, complete shipment documentation in **NCI Medidata Rave.**
     1. Complete the **Shipping Status** form.
        1. Each field in the **Shipping Status** form should be completed as shown below and **Number Sent** (circled below) should equal the number of biopsy passes in the shipment.
        2. **Email Alert** (circled below) is only checked for the last specimen in a shipment if multiple specimens are shipped together.
     2. If there are other specimens to be shipped with the frozen biopsies, use the **Copy Shipping** utility form (shown below) in the other specimens’ folder.

Graphical user interface, text, application

Description automatically generated

* + 1. Print the **Shipping List** report and place it in the box with the specimens.
       1. The **Shipping List** report is found in the report panel at the bottom of the window at the site level (an example shown below) since specimens from multiple patients can be included in a single shipment.

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Graphical user interface, application, Word

Description automatically generated

* + - 1. Shipment should include a hard copy (printed copy) of the **Shipping List**. An example is shown below.

Table

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* + - 1. Shipment should also include a hard copy of the **TISSUE BIOPSY VERIFICATION** form found in the appendices of corresponding protocols.

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* 1. Specimen shipment to EET Biobank
     1. Follow the **Shipping Specimens from Clinic Site to the EET Biobank/ETCTN Biorepository** section of the clinical protocol for general instructions of sample shipment to EET Biobank.
     2. Frozen biopsies should be shipped in kits provided by EET Biobank. The shipping container sent with kit contents should be used to ship specimens to EET Biobank. **Note:** It’s important to include sufficient dry ice to keep the biopsy frozen for at least 96 hours.
     3. Frozen specimens may be shipped on Monday through Thursday to the following address:

EET Biobank

The Research Institute at Nationwide Children's Hospital 700 Children's Drive, WA1340

Columbus, Ohio 43205

PH: (614) 722-2865

FAX: (614) 722-2897

**Note: FedEx Priority Overnight** service is the required shipping method. The EET Biobank FedEx account will not be provided to submitting institutions.

Sites are responsible for all costs for shipments to the EET Biobank, so the overnight express shipment should be billed directly to the shipping institution/site.

* 1. Useful contacts for Specimen Collection, Handling and Shipment:
     1. Send all questions related to this SOP or PD- assay support questions to: [NCI\_PD\_Support@mail.nih.gov](mailto:NCI_PD_Support@mail.nih.gov)
     2. Send all technical questions about the Specimen Tracking System to: [STS.Support@theradex.com](mailto:STS.Support@theradex.com)
     3. EET Biobank queries (kit inquiries and sample shipping): [BPCBank@nationwidechildrens.org](mailto:BPCBank@nationwidechildrens.org)

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**APPENDIX 1: BIOPSY COLLECTION RECORD**

**Note**: This document lists important information to be recorded during the biopsy collection process for later documentation in **NCI Medidata Rave.** The completed document should be filed with the study patient’s other records at a predetermined location according to local policy for managing clinical trial information. Please **do not** include the document in the shipment to EET Biobank**.**

Certified Assay Operator: Facility/Clinic Collecting Specimens: Clinical Protocol Number: Patient ID:

1. **Biopsy Collection Information:**

**Note:** Information collected in the table below will be entered in Medidata RAVE.

**Note:** Record times using military time (24-h designation); for example, specify 16:15 to indicate 4:15 PM.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Pass A** | **Pass B** | **Pass C** | **Pass D** |
| **Specimen ID** |  |  |  |  |
| **Protocol timepoint of biopsy** (Cycle, Day, and Hours post dose, if post treatment) |  |  |  |  |
| **Needle type** |  |  |  |  |
| **Site of biopsy** (complete for all passes or note “same” for replicate cores) |  |  |  |  |
| **Required:**  Time elapsed from collection to placement in tube | min sec | min sec | min sec | min sec |
| **Date biopsy collected** |  |  |  |  |
| **Time biopsy collected** | : | : | : | : |
| **Time biopsy placed in tube** | : | : | : | : |

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1. **Notes, including any deviations from the SOP:**

# APPENDIX K EMBEDDING NEEDLE BIOPSIES

*If your study has sites embedding formalin fixed tissue from needle biopsies in paraffin, include this Appendix. Customize the protocol text and reference this appendix in the body of the protocol.*

**Embedding needle biopsies (FFPE processing):**

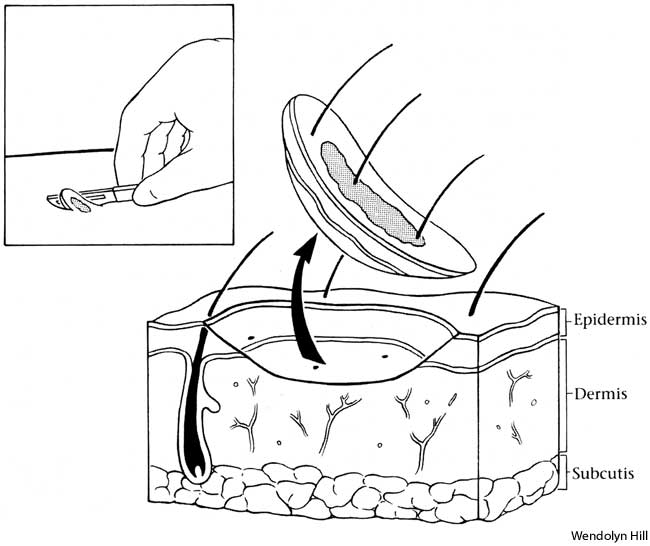
* These types of specimens are very thin and delicate.
* Lift gently with forceps and avoid pinching too roughly to prevent fragmentation and crush artifact.
* Because these specimens are typically very thin (diameter) it is absolutely essential that they be orientated for optimal sectioning.
* They must be embedded in the same plane, as flat as possible (including tips of long strings).
* Please select the mold size that is most suitable and will be easiest for the histotechnician to eventually position multiple FFPE tissue sections on the glass slides.
* Dipping the needle core biopsies in methylene blue or eosin renders the samples more readily visible in the tissue block (helps when tissue sections are being oriented during embedding and eventually cut following FFPE processing).
* Arrange the specimens in a horizontal plane or diagonal plane to reduce the distance that the knife blade travels across the specimen- this may reduce folds and compression.

|  |  |
| --- | --- |
| **Adequate – horizontal**  A diagram showing adequate orientation of needle biopsies in paraffin. Four needle biopsies are arranged side-by-side, all in a horizontal orientation. | **Adequate – diagonal**  A diagram showing adequate orientation of needle biopsies in paraffin. Four needle biopsies are arranged side-by-side, and are all slightly tilted diagonally. |
| **Avoid – no orientation**  A diagram showing an inadequate orientation of needle biopsies in paraffin. Four needle biopsies are arranged haphazardly. |  |

# APPENDIX L CUTTING AND EMBEDDING SKIN

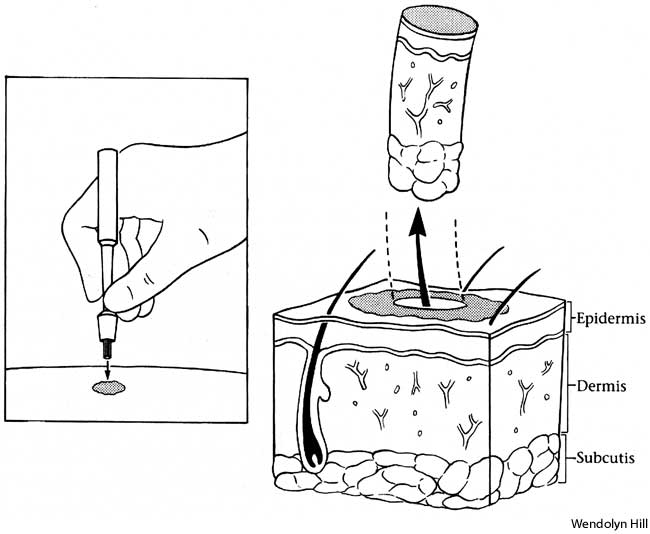
*If your study has sites cutting and embedding skin include this Appendix. Customize the protocol text for your study and reference this appendix in the body of the protocol.*

1. **Skin Specimens - General Considerations for FFPE tissue block preparations: It is crucial to maintain vertical orientation at all times in the sections.** 
   1. Ink can be used to highlight areas of the specimen, including how to orient it when embedding (e.g., inked dermal/subcutaneous margins). Black or blue inks are preferred.
   2. Diagrams should be used for any difficult or complicated biospecimens.
2. **Skin Shave Biopsies**
   1. Principle: Ink the dermal/subcutaneous margins of all skin specimens.



* 1. Processing the Specimen
     1. The specimen type (shave) dimensions (including depth and surface appearance) are described. The specimen is usually oval and relatively flat. The edges may curl secondary to retraction of the dermis. Specimens larger than 4 mm in diameter should be bisected, larger than 6 mm in diameter should be trisected, larger than 8 mm should be quadrisected or serially sectioned, and end sections submitted in a separate cassette. The vertical orientations should be maintained by making cuts perpendicular to the surface at 2-3 mm intervals.
     2. For small shaves < 4mm, the intact specimen should be placed on edge (aka: cut side down) in a cassette.
     3. For larger shaves > 4mm and < 8 mm, the sections should be placed in a single cassette on edge.
     4. For shaves > 8 mm, the sections should be placed in 2 or more cassettes with the ends in 1 cassette.

1. **Skin Punch Biopsies**
   1. Principle: Punch biopsies are performed to completely excise small lesions or to sample large lesions. Punches can range from 2-8 mm in diameter.



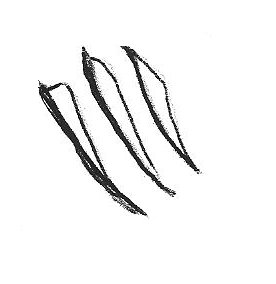
* 1. Processing the specimen
     1. The type of specimen (punch biopsy) is described including diameter, depth, and skin color. Lesions are described including size, type (macular, papular, vesicular, plaque), borders (well-circumscribed, irregular), color, shape (verrucous, lobulated, bosselated).
     2. Apply ink to the cut surfaces of all punch biopsies.
     3. See below instructions for specific sectioning details

|  |  |
| --- | --- |
| Punch Biopsy < 4mm in diameter  **Diagram of a punch biopsy** | Lay specimen on its side intact in a cassette |
| Punch Biopsy > 4mm in diameter | Bisect punch lengthwise and place both halves with cut surface from middle of specimen face down in cassette. |

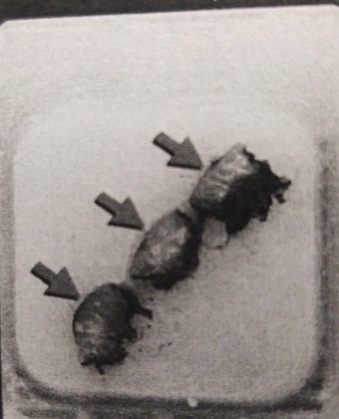
**Embedding – Summary**

**Skin shave biopsies**

Orientation: Embed the cut surface of the skin sliver to be positioned perpendicularly so that all layers will be displayed. Shave biopsies often will resemble “crescent” shapes when embedded. Use the epidermal surface to assist orientation.



When a specimen is inked, all inked edges should face the same direction in the block face.



**Skin punch biopsies - not bisected:**

Orientation: Embed with the long side with epidermal disc on edge to show epidermis, dermis and subcutaneous fat layer in cross-section. The skin pieces should be placed at a slight angle with the epidermis facing all in the same direction (multiple pieces). The specimen and the epidermis must be pressed to lie in the same plane. The entire epidermal edge must be present on the completed slides.

**Skin punch biopsies - bisected**

Orientation: Embed cut surfaces down, long side with epidermal disc on edge to show epidermis, dermis and subcutaneous fat layer in cross-section.

**Notes:**

1. Many times, special instructions for embedding are noted, especially if the histology laboratory has a specific SOP for embedding skin lesions.
2. Identify the tissue in the cassette. Use submitted descriptions regarding the gross appearance of the biopsied specimen (e.g., features of the lesion may include color, ulceration, polypoid configuration).
3. Check if the specimen was inked and if there is a description of the reason for inking (e.g., identify the cut surface or the dermal/subcutaneous margin). If the specimen is inked be sure to follow embedding instructions (e.g., inked side down).
4. Choose a mold that is of adequate size for the dimensions of the tissue.
5. If you re embedding very small samples, use a magnifying glass to arrange them on edge.
6. If the edges of the skin specimen curl due to retraction (commonly seen with shave biopsies), uncurl the tissue gently with forceps and warm them on the embedding center before embedding on edge. Skin shave biopsies should be straightened before paraffin hardens completely.

**Slide preparation -** The FFPE tissue block will be trimmed or “faced” until the full outline of the tissue is visible. Cut at 3-4 microns.

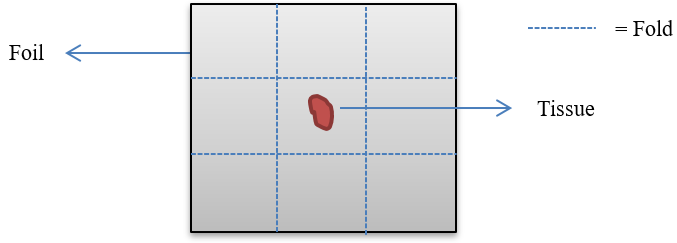
For layered skins (e.g., skin shave biopsies >4 mm), the epidermis should be facing toward the embedding unit, cassette number facing to the right. The skin pieces should be placed at a slight angle with the epidermis facing all in the same direction (multiple pieces). The specimen and the epidermis must be pressed to lie in the same plane. The entire epidermal edge must be present on the completed slides.

# APPENDIX M EMBEDDING TISSUE USING OPTIMAL CUTTING TEMPERATURE (OCT) COMPOUND

*If your study has sites embedding tissue using OCT include this Appendix. Customize the protocol text for your study and reference this appendix in the body of the protocol.*

* + 1. Prepare a laboratory workstation for embedding the tissue. Clean forceps and scalpels with 10% bleach followed by 95% ethanol. Allow them to dry. Obtain a clean dry ice bin (or clean one with a water based broad spectrum antimicrobial disinfectant and cleaner that meets CDC guidelines for intermediate level disinfectant). Scoop dry ice into the bin and cover the top of the bin completely with foil.
       1. Obtain a cryomold and a labeled mega cassette (these cassettes offer double the depth of conventional cassettes and allow the embedding and processing of larger tissue sections that do not fit standard-size cassettes).
       2. Place a small amount of OCT Compound on the bottom of the cryomold.
       3. Place the cryomold onto the room temperature cutting board.
          1. If the tissue is snap-frozen, then place the snap-frozen tissue on a petri dish on the foil covered dry ice. Don’t remove the snap-frozen tissue from the foil covered dry ice tray to avoid thawing.
          2. If the tissue is fresh, then place the fresh tissue on a piece of gauze on a clean, room temperature cutting board.
    2. Anchor the tissue using clean forceps.
       1. Cut a section to be embedded in OCT Compound from the received tissue using a clean scalpel and a new blade.
       2. Place the cut piece of tissue in the cryomold containing the small amount of OCT Compound with the cut surface down. Move the cryomold to the foil covered dry ice bin.
       3. Gently press the cut piece of tissue toward the bottom of the mold using clean forceps so that the tissue is flat against the bottom of the cryomold. Ensure the orientation of the tissue is correct for the tissue type.
       4. The cryomold will begin to freeze. Once the tissue is adherent to the bottom of the mold, remove the forceps.
    3. Fill the remainder of the cryomold with OCT compound. Do not allow the cryomold to completely freeze before adding the remainder of the OCT.
    4. Freeze the cryomold by placing it onto foil covered dry ice or place into a device where the sample can be cooled by LN2 vapor (e.g., cryocart).
       1. Do not place cryomold with the tissue (or the tissue sample) in the liquid phase of LN2
       2. Ensure that the cryomold sits flat and is not slanted.
    5. Remove the cryomold containing the now solidified OCT-embedded frozen tissue block from the dry ice (or the LN2 vapor phase) once the block has turned white and completely solid.
    6. Remove the OCT embedded frozen tissue block from the cryomold.
       1. Allow the cryomold to warm very slightly so that the OCT-embedded frozen tissue can be removed from the cryomold without cracking. One technique is to gently rub the back of the cryomold with your gloved thumb until the mold is slightly pliable. Then press on the mold and pop the OCT-embedded frozen tissue block out.
    7. Neatly wrap the OCT embedded frozen tissue block in a piece of foil by folding the foil in thirds around it. Refer to Figure 1.
    8. Place the OCT-embedded frozen tissue block wrapped in foil in a labeled mega cassette and close the lid.
    9. Keep the mega cassette on the foil covered dry ice bin until placing in a liquid nitrogen vapor phase freezer (preferred) or -80°C freezer.

Fig.1



# APPENDIX N EMBEDDING TISSUE FOR CRYOSECTIONING USING OPTIMAL CUTTING TEMPERATURE (OCT) COMPOUND

*Include this appendix only if your study has sites embedding tissue for cryosectioning using OCT. Customize the protocol text for your study and reference this appendix in the body of the protocol.*

Fixation and heat involved in routine histologic processing can inactivate many antigens and genetic material within the tissue, therefore frozen sections must be used. This procedure is specific for embedding fresh tissue in OCT Compound in order to obtain frozen tissue sections using a cryostat. Unstained frozen tissue sections may be used for subsequent staining; scrolls can be also generated by this method and used for gene sequencing.

Tissue should be frozen as promptly as possible after removal from the body to avoid morphological distortions and damage due to:

* Tissue drying artifact.
* Autolysis: The destruction of tissues or cells by the action of substances, such as enzymes, that are produced within the organism. Also called self-digestion.
* Putrefaction: Decomposition by microorganisms

The object is to freeze so rapidly that the water present in the tissue does not have time to form crystals and remains in a vitreous form that does not expand when solidified.

* Slow freezing can cause distortion of tissue due to ice crystal formation that replaces the architecture with a “Swiss Cheese” effect.
* Don’t submerge the tissue in liquid nitrogen (LN2) as it creates a vapor barrier that causes freezing in a slower, unpredictable pattern resulting in tissue artifacts that prevent accurate histological evaluation.

**Embedding fresh tissue in OCT Compound prior to sectioning using a cryostat**

1. Have only one sample at a time in the cryostat.

* Try to keep the section up to one square cm in greatest dimension.
* Fatty tissues (e.g., breast) and hard tissues (e.g., myometrium) may be difficult to cut when using this method, so smaller representative samples are recommended in some cases.
* Carefully remove excess liquid surround the tissue by absorption with Kim-wipe® or paper towel prior to freezing (don’t press the tissue too hard while doing this). Excess liquid will form ice crystals on the tissue surface and prevent the attachment to the OCT compound.

2. Check temperature of cryostat chamber before starting the process.

* The optimal temperature for cryostat sectioning depends on the nature of the tissue.
* Most tissues are routinely sectioned when that cryostat chamber temperature reaches

-20°C degrees.

3. Place clean paintbrushes and cryostat block (chuck) in the cryostat chamber, attach blade, and screw glass cover into place about 20 minutes prior to sectioning. This allows all material to equilibrate to the cryostat chamber temperature of -20°C.

4. Obtain a cold cryostat block (chuck), place a few drops of OCT Compound on its flat surface.

* Orient the sample on the surface of the OCT film, lightly pressing the cut piece of tissue toward the OCT medium using clean forceps so that the tissue is flat against it and allow the tissue to freeze in the cryostat chamber for several minutes.
* Once frozen, pour enough OCT to cover the sample and allow it to freeze for up to 5 minutes\*.

*\*If you need to expedite the freezing process, you can expose the OCT embedded tissue to LN2 vapor, but never drop the tissue in the liquid phase of the LN2.*

5. Attach the cryostat block (chuck) with the OCT embedded frozen tissue sample into the cryostat chamber unit designed to hold it (this varies depending on the model of the cryostat).

* Be sure that the cryostat block (chuck) is screwed in place.
* Follow instructions to cut the frozen tissue sections and either mount them on prelabeled glass slides or (if preparing scrolls) put them in a prelabeled cold resistant vial with a removable top.

6. After all sections are cut, keep frozen sections cold in the cryostat chamber. After the entire sample is sectioned, store slides or scrolls in a freezer at the previously determined storage temperature or follow the instructions for staining them (e.g., with eosin and hematoxylin).