## Specific Instructions for the Use of Organ Dysfunction Templates

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. These organ dysfunction templates are designed to evaluate toxicity and to measure pharmacokinetic and pharmacodynamic parameters in each of 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](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072127.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 Cockroft-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. All sections may be modified as necessary to meet the scientific aims of the study and development of the protocol.

1. Each protocol template consists of two parts:

1. Protocol Submission Worksheet: available at

[http://ctep.cancer.gov/protocolDevelopment/docs/psw.doc](%20http://ctep.cancer.gov/protocolDevelopment/docs/psw.doc). 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.

2. The Protocol Submission Worksheet and Protocol Template documents should be completed, and both documents (including the Appendices) should be submitted to CTEP for review.

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.

4. All protocol template instructions and prompts are in *italics*. Blank space or \_\_\_\_\_\_\_\_ indicates that you should fill in the appropriate information. **As you complete the information requested, please delete the italicized text.**

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

6. For problems or questions encountered when using these documents (Protocol Submission Worksheet or Protocol Template), please contact the CTEP help desk by telephone (301-840-8202), fax (301-948-2242), or e-mail ([ncictephelp@ctep.nci.nih.gov](file:///\\ctepdc02\data\Protocol%20Templates\Templates_Generic%20Protocols\Generic%202009%20-%20in%20progress\ncictephelp@ctep.nci.nih.gov)).

**NCI Protocol #:** *To be assigned by the NCI. For cooperative group studies, the NCI will utilize the local group protocol #.*

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

**TITLE:** A Phase 1 and Pharmacokinetic Single Agent Study of  *Study Agent* in Patients with Advanced Malignancies and Varying Degrees of Liver Dysfunction

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

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

**\*Principal Investigator:** *Name*

*Address*

*Address*

*Telephone*

*Fax*

*e-mail address*

**Co-Investigators:** *Name*

*Address*

*Address*

*Telephone*

*Fax*

*e-mail address*

*Name*

*Address*

*Address*

*Telephone*

*Fax*

*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 Web site for a complete description of the* ***Principal Investigator's*** *responsibilities (*[*http://ctep.cancer.gov/investigatorResources/default.htm#Investigators\_handbook*](http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm)*).*

***The Principal Investigator and all physicians responsible for patient care must have a current FDA Form 1572, Supplemental Investigator Data Form (SIDF), Financial Disclosure Form (FDF), and CV on file with the NCI.*** *Failure to register all appropriate individuals could delay protocol approval. If you are unsure of an investigator's status, please contact the Pharmaceutical Management Branch, CTEP at (301) 496-5725 or by e-mail at* [*PMBRegPend@ctep.nci.nih.gov*](mailto:PMBRegPend@ctep.nci.nih.gov)*. Please indicate, on the title page, if an Associate Investigator is NOT responsible for patient care and therefore does not require a current 1572, SIDF, FDF, and CV on file.*

*If this is a multi-institution study, the protocol title page should include the name of each participating institution, the investigator responsible for the study at that institution, and his/her phone # and e-mail address. (This requirement does not apply to Cooperative Group studies*.)

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 the Canadian Health Products and Food Branch (HPFB) for their participation in the study. A Canadian investigator should be designated to be responsible for preparing and submitting the CTA to the Canadian HPFB 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>. A copy of the “No Objection” letter should be forwarded to the Pharmaceutical Management Branch at (fax) 301-402-0429 when available.

**Statistician:****Study Coordinator:**

*(if applicable) (if applicable)*

*Name Name*

*Address Address*

*Address Address*

*Telephone Telephone*

*Fax Fax*

*e-mail address e-mail address*

**Responsible Research Nurse: Responsible Data Manager:**

*Name Name*

*Address Address*

*Address Address*

*Telephone Telephone*

*Fax Fax*

*e-mail address e-mail address*

**NCI Supplied Agent**: *CTEP IND Agent (NSC #; IND #, if available)*

**Protocol Type / Version # / Version Date:** \_\_\_*Type / Version # / Version Date*\_\_\_\_

*(Protocol types: Original, Revision, or Amendment)*

**SCHEMA**

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, E: liver transplant) 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** | **Group E**  **Liver**  **Transplant** |
| Total  Bilirubin | ≤ ULN | B1: ≤ ULN  B2: >1.0x – 1.5x ULN | >1.5x – 3x ULN | >3x ULN | Any |
| SGOT/AST | ≤ ULN | B1: > ULN  B2: Any | 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.)*

*Study 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 liver function** (*units)*  \* | **Mild liver dysfunction** (*units)* \* | **Moderate liver dysfunction**  (*units)*  **\*** | **Severe liver dysfunction** (*units)* \* | **Liver transplant** (*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 5.1.1 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 5 and 6.**

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**1. OBJECTIVES**

1.1. **Primary Objectives**

* To establish the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of *(Study Agent)*  in groups of patients with varying degrees of hepatic dysfunction (mild, moderate, severe, and liver transplant) in order to provide appropriate dosing recommendations for *(Study Agent)*  in such patients.
* To characterize the pharmacokinetic (PK) and pharmacodynamic profiles of *(Study Agent)* in patients with varying degrees of hepatic dysfunction.

1.2. **Secondary Objectives**

* To document the non-DLTs associated with administration of (*Study Agent)*  in patients with hepatic dysfunction.
* To correlate the Child-Pugh classification of hepatic dysfunction with the observed toxicities, plasma PK, and PD of *(Study Agent)*  administration.
* To document any antitumor activity associated with  *Study Agent*  treatment of patients enrolled on this study.

**2. BACKGROUND**

2.1**CTEP IND Agent**

*Please provide background information below on the CTEP IND study agent, including the mechanism of action, summaries of nonclinical and clinical studies, nonclinical and clinical PK, safety profile, and the rationale for the proposed starting doses and dose escalation scheme. Please clearly indicate if the liver or kidney is known to be the major route of elimination. If available, please include information on the metabolism of the study agent in humans and its potential for hepatic, metabolic, or drug interactions (*e.g.*, via the P450 enzyme system).*

2.2 **Rationale for a Phase 1 Study in Patients with Hepatic Dysfunction**

*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>

2.3 **Child-Pugh Classification (CPC)**

*The CPC 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; Shaad 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*  *(Study Agent)* *. A copy of the CPC is provided in Appendix A.*

**3. PATIENT SELECTION**

3.1 **Eligibility Criteria**

3.1.1 *Please select the appropriate text below depending on the agent under study 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.

* 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.

* 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.

3.1.2 Age >18 years.

3.1.3 ECOG performance status <2 (Karnofsky >60%, see Appendix B).

3.1.4 Life expectancy of >3 months.

3.1.5 Patients must have acceptable renal and marrow function as defined below:

- leukocytes >3,000/mcL

- absolute neutrophil count >1.5 xL

- platelets >100 x 109/L

- creatinine within normal institutional limits

OR

- creatinine clearance > 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal.

3.1.6Patients with abnormal liver function will be eligible and will be grouped according to the criteria in Section 5.1. 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. Liver function tests should be repeated within 24 hours prior to starting initial therapy.

* + 1. 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 (*Study 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.

3.1.8 Eligibility of patients receiving any medications or substances known to affect or with the potential to affect the activity or PK of *(Study Agent)*  will be determined following review of their case by the Principal Investigator and the CTEP senior investigators. Efforts should be made to switch patients with gliomas or brain metastases who are taking anticonvulsant agents to other medications. (A list of medications and substances known or with the potential to interact with selected CYP450 isoenzymes is provided in Appendix C.)

3.1.9 *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 IND Agent* administration.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 **Exclusion Criteria**

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. 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.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to  *CTEP IND Agent* .

3.2.5 *Please state appropriate exclusion criteria relating to concomitant medications or substances that have the potential to affect the activity or pharmacokinetics of the study agent(s). Examples of such agents or substances include those that interact through the CYP450 isoenzyme system or other sources of drug interactions (*e.g.*, P-glycoprotein). Specifically excluded substances may be listed below, stated in Section 8 (Pharmaceutical Information), and presented as an appendix. If appropriate, the following text concerning CYP450 interactions may be used or modified.*

Patients receiving any medications or substances that are inhibitors or inducers of *specify CYP450 enzyme(s)* are ineligible. Lists including medications and substances known or with the potential to interact with the *specified CYP450 enzyme(s)*  isoenzymes are provided in *Appendix (#/letter)*.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 *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 Web site (*[*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* .

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

HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with *CTEP IND Agent* . In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated. 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.

3.2.9 *Please insert other appropriate agent-specific exclusion criteria.*

3.3 **Inclusion of Women and Minorities**

Both men and women of all races and ethnic groups are eligible for this trial.

1. **REGISTRATION PROCEDURES**

*This section should be marked “N/A” if this study is being performed within a single institution. For multi-institutional studies, suggested text is provided below which may be modified as necessary. Appropriate forms for the study (*e.g.*, Eligibility Screening Worksheet, Registration Form) should be developed and included with the protocol. These forms must be used by all participating institutions for data submission.*

* 1. **General Guidelines**

Eligible patients will be entered on study centrally at the *(Coordinating Center)* by the Study Coordinator. All sites should call the Study Coordinator *(Telephone #)*  to verify dose level availabilities. The required forms (Eligibility Screening Worksheet and Registration Form) can be found in Appendix F.

Following registration, patients should begin protocol treatment within 5 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 Organ Dysfunction Working Group Coordinator should be notified of cancellations as soon as possible.

*[\*Note: This can be edited for leukemia protocols where treatment should be started as rapidly as possible.]*

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 ([PIO@ctep.nci.nih.gov](mailto:PIO@ctep.nci.nih.gov)).

* 1. **Registration Process**

To register a patient, the following documents should be completed by the research nurse or data manager and faxed  *(Fax # )* or e-mailed  *(e-mail address)*  to the Organ Dysfunction Working Group Coordinator:

* Eligibility Screening Worksheet
* Registration Form
* Copy of required laboratory tests
* Signed patient consent form
* HIPAA authorization form (signed by patient)

The research nurse or data manager at the participating site will then contact the Coordinator at *(Telephone #)*  or by e-mail at *(e-mail address)*  to verify eligibility. To complete the registration process, the Coordinator will

* assign a patient study number
* register the patient on the study
* assign the patient a dose
* fax or e-mail the patient study number and dose to the participating site
* call the research nurse or data manager at the participating site and verbally confirm registration.

**5. TREATMENT PLAN**

5.1 **Stratification by Hepatic Dysfunction**

5.1.1 Study Definition of Hepatic 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, E: liver transplant) 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** | **Group E**  **Liver**  **Transplant** |
| Total  Bilirubin | ≤ ULN | B1: ≤ ULN  B2: >1.0x – 1.5x ULN | >1.5x – 3x ULN | >3x ULN | Any |
| SGOT/AST | ≤ ULN | B1: > ULN  B2: Any | 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.
* Group E (liver transplant): Patients with liver transplants should be stratified for dosing purposes to the group (B1, B2, C, or D) in which their total bilirubin and SGOT/AST levels match or are better than the criteria defined for non-transplant patients. Patients continuing to receive immunosuppression for active graft-versus-host-disease should be treated using the current Group D dose level.
* 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 5.3 will not apply and a recommended dose will not be defined in these patients.

5.1.2 Child-Pugh Classification (CPC) of liver dysfunction

Each patient’s CPC score should be calculated at baseline and prior to each treatment cycle. See Appendix A for instructions on CPC calculation.

5.2 **Agent Administration**

*Please state the route and schedule of (Study 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 liver function testing within 24 hours before drug administration and maximum PK sampling within a standard working week, the first dose of *(Study 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 Web site (*[*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 Sections 5.4 (dose escalation scheme) and 5.4.1 (dose escalation rules). The dose may be reduced for individual patients in subsequent cycles depending on toxicity (Section 6.2). 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 *(Study Agent)*  are described in Section 7.1. Appropriate dose modifications for *(Study Agent)*  are described in Section 6.2. No investigational or commercial agents or therapies other than those described in Section 5.0 (Treatment Plan) may be administered with the intent to treat the patient’s malignancy.

5.3 **Definition of Dose-Limiting Toxicity**

Toxicities will be graded according to the Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP Web site at <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>. Treatment-related events occurring during the first cycle of treatment are considered DLTs.

*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 hepatic dysfunction studies. Suggested text is provided below.*

The following treatment-related adverse events are considered dose limiting for all hepatic 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.
* Liver toxicity

Note: Investigators should use their best judgment based on clinical and radiological criteria to exclude progressive disease as the cause of increased hepatic dysfunction.

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

- Patients in moderate dysfunction group (Group C): 1.5 times increase from baseline total bilirubin to level defined for the severe group lasting for >2 weeks

- Patients in severe dysfunction group (Group D): 1.5 times increase from baseline value of total bilirubin for >2 weeks

* 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.
* Treatment delays of ≥2 weeks due to treatment-related toxicity will constitute a DLT.

Management and dose modifications associated with the above adverse events are outlined in Section 6.2. Dose escalation will proceed within each group according to the rules stated in Section 5.4.

5.4 **Dose-Escalation Scheme**

*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.)*

*Study 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 liver function** (*units)* **\*** | **Mild liver dysfunction** (*units)* \* | **Moderate liver dysfunction** (*units)* \* | **Severe liver dysfunction** (*units)* \* | **Liver transplant** (*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 5.1.1 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.

5.4.1 Dose Escalation Rules

* Dose escalation will proceed within each hepatic dysfunction group according to the scheme outlined in Section 5.4. DLT is defined above (Section 5.3).
* 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.

5.4.2 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.

5.4.3 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 will be accrued to this dose level.

5.4.4 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 9 or 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. |

5.4.5 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. |

5.5 **General Concomitant Medication and Supportive Care Guidelines**

*Please state guidelines for use of concomitant medications or any additional appropriate supportive care medications or treatments. Specifically:*

* Patients should be cautioned about the concomitant use of acetaminophen (Tylenol®, Percocet®, or other analgesic combination tablets containing acetaminophen).
* *Please indicate any other medications that should be avoided during this evaluation of \_ (Study Agent)* *in patients with hepatic dysfunction.*
* *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 \_*Study 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.

5.6 **Duration of Therapy**

In the absence of treatment delays due to adverse events, 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, or
* General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.7 **Duration of Follow-Up**

Patients will be followed for *weeks*  after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.8 **Criteria for Removal from Study**

Patients will be removed from study when any of the criteria listed in Section 5.7 applies. The reason for study removal and the date the patient was removed must be documented in the CRF.

**6. DOSING DELAYS/DOSE MODIFICATIONS**

* 1. **Retreatment Criteria**

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

* absolute neutrophil count ≥1.5 x 109/L
* platelets ≥100 x 109/L
* creatinine ≤1.5 x upper limit of normal
* 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 function is NOT required prior to retreatment provided the decline is considered disease-related. However, patients who have *Study Agent*-induced deterioration of hepatic function should not be retreated and should be removed from the study.

For patients whose hepatic 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.

* 1. **Dose Modification Guidelines**

The dose of  *Study 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 function group at the time of retreatment:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 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 |

*\* 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.*

* Patients should thus be retreated at the current dose level for the hepatic 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 5.4.2.
* Collection of pharmacokinetics from patients who change dose level and/or hepatic 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.

**7. 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 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via AdEERS) **in addition** to routine reporting.

7.1 **Comprehensive Adverse Events and Potential Risks List (CAEPR)**

*The Comprehensive Adverse Event and Potential Risks (CAEPR) list for CTEP-supplied agent will be provided with the LOI approval letter. Sections provided below should be used or deleted as necessary. Adjust the heading levels as appropriate (*e.g.*, if this template is being used for a single-agent protocol, the subsections below can be deleted, and the CAEPR for that agent inserted directly under heading 7.1).*

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse\_events\_adeers for further clarification.

*The CAEPR may not provide frequency data; if not, refer to the Investigator’s Brochure for this information.*

**NOTE**: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously via AdEERS. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPR for CTEP IND Agent

7.2 **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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site <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 7.1.1) should be reported through AdEERS only if the grade is above the grade provided in the SPEER.
  + Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.
* **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.

7.3 **Expedited Adverse Event Reporting**

7.3.1 Expedited AE reporting for this study must use AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP Web site (<http://ctep.cancer.gov>). 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 Web site ([http://ctep.cancer.gov](http://ctep.cancer.gov/reporting/adeers.html)). These requirements are briefly outlined in the tables below (Section 7.3.3).

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 AdEERS by the original submitter at the site.

7.3.2 *The following text is required for multi-institutional studies only and may be deleted for single institution studies.*

AdEERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. AdEERS provides a copy feature for other e-mail recipients. **All AEs reported via AdEERS must be copied to the Organ Dysfunction Working Group Coordinator (\_\_*e-mail*\_\_) using the copy feature of AdEERS.**

7.3.3 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, unless as noted below. Attribution to treatment or other cause must be provided.**

Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)”**under the system organ class (SOC) of the same name. 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 AdEERS 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 reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.   + “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE. | |
| 1Serious adverse events that occur **more than** 30 days after the last administration of investigational agent/intervention 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 AdEERS 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 reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. * “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE. | | |
| 1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:  **Expedited 24-hour notification followed by complete report within 5 calendar days for:**   * All Grade 3, 4, and Grade 5 AEs   **Expedited 10 calendar day reports for:**   * Grade 2 AEs resulting in hospitalization or prolongation of hospitalization   2 For 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 AdEERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **CTCAE SOC** | **Adverse Event** | **Grade** | **Hospitalization/ Prolongation of Hospitalization** | **Attribution** | **Comments** |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

7.4 **Routine Adverse Event Reporting**

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through AdEERS must also be reported in routine study data submissions.**

7.5 **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 via AdEERS. 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.

7.6 **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 reporting via CDUS unless otherwise specified.

**8. PHARMACEUTICAL INFORMATION**

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

*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.*

8.1 ***CTEP IND Agent***

***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.*

8.2 **Availability**

*CTEP IND Agent*  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*  is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.3 **Agent Ordering and Agent Accountability**

8.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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 investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (<https://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an “active” account status and a “current” password. Alternatively, site personnel can fax completed Clinical Drug Requests (NIH-986) to the Pharmaceutical Management Branch at (301) 480-4612. For questions about drug orders, transfers, returns, or accountability, call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) anytime.

8.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator’s Handbook for Procedures for Drug Accountability and Storage.)

**9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES**

*Please briefly describe all planned correlative studies with reference to the “Guidelines for Correlative Studies in Clinical Trials” provided with the LOI response and available on the CTEP Web site (*[*http://ctep.cancer.gov/protocolDevelopment/default.htm#ancillary\_correlatives*](http://ctep.cancer.gov/protocolDevelopment/default.htm#ancillary_correlatives)*).* ***Explicit instructions for handling, preserving, and shipping the specimens should be provided below****. Information on endpoint validation including additional background (as needed), description of the assay(s) used, materials and methods, and assay validation should be provided in an appendix. A plan for statistical analysis of the results of the correlative study(ies) should be provided in Section 13.4, Analysis of Secondary Endpoints.*

*If development of diagnostic assays to identify patients who might benefit from a molecularly targeted therapy is planned, validation in a central reference laboratory, tissue banking, and standardization of procedures is of high importance. If samples will be shipped to a central laboratory for processing and analysis, responsible parties and contact information should be provided below in addition to instructions for handling, preserving, and shipping the specimens.*

*A correlative study title using meaningful descriptive text should be provided for each planned correlative study using the Protocol Submission Worksheet found on the CTEP Web site (*[*http://ctep.cancer.gov/protocolDevelopment/default.htm*](http://ctep.cancer.gov/protocolDevelopment/default.htm)*). These titles will facilitate documentation of contributions to basic science in the context of the clinical trial.*

*A suggested format for presentation of the required information is shown below and may be used or modified as required. 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.*

9.1 **Pharmacokinetic Studies**

Pharmacokinetic 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 *Agent Manufacturer/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 hepatic 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 13.5.

9.1.1 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.*

9.1.2 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 |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

9.1.3 Blood Sample Processing Procedures

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

9.1.4 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.*

9.2 **Biomarker Studies**

*If the protocol includes any biomarker studies using* in situ *hybridization (ISH) and/or immunohistochemistry (IHC) techniques, fill out the “ISH Biomarker Template” and/or the “IHC Marker Template,” as appropriate, and attach to this protocol submission as separate Appendices. These templates are sent with LOI approval letters for any protocols using these methods, and can also be downloaded from the CTEP website (*[*http://ctep.cancer.gov/protocolDevelopment/default.htm#ancillary\_correlatives*](http://ctep.cancer.gov/protocolDevelopment/default.htm#ancillary_correlatives)*).*

*Biomarker studies should be summarized in this section. Please specify whether these studies are “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/regs/toc.aspx*](http://wwwn.cdc.gov/clia/regs/toc.aspx)*).*

*The description for all proposed biomarker studies, if applicable, should include specific information, as outlined below.*

1. *Provide a hypothesis and rationale for biomarker utility and a description of the impact on therapeutic agent development based on the following considerations:*
   1. *Biological and/or mechanistic rationale with data to support relationship between biomarker and agent effects*
   2. *Intended use within the proposed study*
   3. *Preclinical in vitro and in vivo, and clinical results, if applicable*
2. *Describe the assay method’s validity and appropriateness for the study*
3. *Describe the investigator’s experience and competence with the proposed assays*
4. *Provide the data supporting the degree of biomarker “fit for purpose” and clinical qualification*
5. *Justify the number of patients and specimens:*
   1. *To demonstrate feasibility*
   2. *To demonstrate that studies are likely to produce interpretable and meaningful results*
6. *Give thoughtful consideration to the risk to the patient of obtaining samples, specimens, or data for biomarker studies in the context of data on biomarker validity and degree of clinical qualification*

9.3 **Laboratory Correlative Studies**

9.1.1 (*Title – Laboratory Correlative Study #1*)

9.1.1.1 Collection of Specimen(s)

9.1.1.2 Handling of Specimens(s)

9.1.1.3 Shipping of Specimen(s)

9.1.1.4 Site(s) Performing Correlative Study

9.1.2 (*Title – Laboratory Correlative Study #2*)

9.1.2.1 Collection of Specimen(s)

9.1.2.2 Handling of Specimens(s)

9.1.2.3 Shipping of Specimen(s)

9.1.2.4 Site(s) Performing Correlative Study

9.4 **Special Studies**

9.2.1 (*Title – Special Correlative Study #1*)

9.2.1.1 Outcome Measure

9.2.1.2 Assessment

9.2.1.2.1 Method of Assessment

9.2.1.2.2 Timing of Assessment

9.2.1.3 Data Recording

9.2.1.3.1 Method of Recording

9.2.1.3.2 Timing of Recording

**10. 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 |  |  |  |
| Child-Pugh classification (CPC) 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 studies |  | Xd----------------------------------------------------------------------------------Xd | | | | | | | | | | | |  |
| *Other tests, as appropriate* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *Other correlative studies* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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], sodium.  b: Serum pregnancy test (women of childbearing potential).  c: Off-study evaluation.  d: Pharmacokinetic samples taken per schedule in Section 9.1. | | | | | | | | | | | | | | |

11**. 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 solid tumor 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.

11.1 **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.

11.1.1 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.

11.1.2 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 by chest x-ray or as >10 mm 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 in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 or pathological lymph nodes with ≥10 to <15 mm 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.

11.1.3 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 lesionsClinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm 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-rayLesions 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 or less. If 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).

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.

11.1.4 Response Criteria

11.1.4.1Evaluation 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.

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. (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.

11.1.4.2 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 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).

11.1.4.3Evaluation 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 | | |

11.1.5 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.

11.1.6 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.*

11.1.7 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.*

11.2 **Antitumor Effect – Hematologic Tumors**

*Please provide appropriate criteria for evaluation of response and methods of measurement.*

11.3 **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.*

**12. DATA REPORTING / REGULATORY REQUIREMENTS**

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

* 1. **Data Reporting**

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Information on CTMS reporting is available at <http://www.theradex.com/CTMS/ctmsmenu.htm>. Data will be submitted to CTMS at least once every two weeks on the NCI/DCTD case report form or the electronic case report form (ACES). CTEP will arrange for a bi-weekly toxicity report to be generated by Theradex, and this report will be provided to the Principal Investigator, all Co-Investigators, and the Organ Dysfunction Working Group Coordinator for the purposes of monitoring and coordination of this multicenter trial.

The final study report should contain all raw data collected during the trial including the case report forms as well as all clinical, laboratory, pharmacokinetic, and pharmacodynamic data collected. This report will be made available to the FDA as well as all members of the Organ Dysfunction Working Group.

* + 1. Responsibility for Data Submission

*Suggested text is provided below which can be modified as necessary. If this study is being performed within a single institution, this section should be marked “N/A” and the text below deleted.*

For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

* 1. **Data Monitoring and Safety Plan**

A mandatory conference call will take place every other week on \_*(day of week)*\_ at \_*(time of day)*\_ (Eastern Time) unless unforeseen events require postponement or cancellation. The call will update participants on the current status of the trial and will include investigators from all participating centers, CTEP, and representatives from \_*(Agent Manufacturer)*\_. At this time, any serious toxicities encountered will be discussed and appropriate action taken, and issues relating to the protocol, treatment, management, or other matters of importance that arise during the conduct of the study will be discussed. Between these regularly scheduled conference calls, unusual toxicities may be discussed among the Principal Investigator and CTEP senior investigators; however, all participants will routinely be updated on such calls via e-mail.

* 1. **CTEP Multicenter Guidelines**

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.

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.

12.4 **Collaborative Agreements Language**

*If the investigational 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 investigational 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.

**13. STATISTICAL CONSIDERATIONS**

13.1 **Study Design**

This phase 1 trial will use a design involving five parallel groups or cohorts of patients with different degrees of liver dysfunction.

* The dose escalation rules used in this study, as detailed in Section 5.4.1, 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 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 liver dysfunction cannot be greater than that for a group with a lesser dysfunction. Section 5.4 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 liver dysfunction groups.
* A maximum of 12 patients (1 per participating institution) will be entered into group A (normal liver 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 impairment at which dose modifications of  *(Study Agent)*  are required, data will be combined across hepatic dysfunction groups to evaluate the association between *(most common/most severe toxicity)* , dose, and liver assay level(s). The outcome variable, *(most common/most severe toxicity)* , will be modeled as function of dose and liver assay 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.*, result in ANC < 1000) for a patient with a given liver function profile.

* Toxicity will be graded according to the Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) (identified and located on the CTEP Web site 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 of all patients will be collected at baseline and will be correlated to the toxicities, PK and PD data seen with *(Study Agent)*  in an exploratory analysis.
* The PK variables described in Section 13.5 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.

13.2 **Endpoints**

13.2.1 Primary

The primary endpoints of this study are as follows:

* Determination of the MTD and DLT of *(Study Agent)*  in groups of patients with varying degrees of hepatic dysfunction (mild, moderate, severe and liver transplant) in order to provide appropriate dosing recommendations for *(Study Agent)*  in such patients.

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 *(Study Agent)* .

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

* 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 *(Study Agent)*  are observed.

13.2.2 Secondary

A secondary endpoint of this study is to calculate the CPC score of each patient at baseline and prior to each cycle and to attempt to correlate these values with the effect of *Study Agent*  on the patient’s observed toxicities, plasma PK, and pharmacodynamic parameters.

13.3 **Sample Size/Accrual Rate**

*Please specify the planned sample size and accrual rate (e.g., patients/month)*.

A minimum of 2 and a maximum of 12 patients will be accrued in each group at each dose level, with 12 patients entered at the recommended dose level in each group. Thus, Group A will accrue 12 patients, while Groups B-E will accrue approximately 15-30 patients each for a total accrual of 72-132 patients. The trial is expected to accrue patients at a rate of approximately 5 patients per month. Group A will be limited to 12 patients, who can be accrued rapidly

13.4 **Stratification Factors**

Patients will be stratified according to level of hepatic dysfunction as described in Section 5.1. Dose escalation and determination of the MTD will be carried out separately for each stratum.

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

13.5 **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 be given.*

**REFERENCES**

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

Informed Consent Template for Cancer Treatment Trials

**(English Language)**

**\*NOTES FOR INFORMED CONSENT AUTHORS:**

1. Model text suggested for use in the informed consent form is in **bold**. It is recommended that the **bold** text be retained when adapting the template to a specific protocol.
2. Instructions and examples for informed consent authors are in *[italics]*.
3. A blank line, \_\_\_\_\_\_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
4. The term ‘study doctor’ has been used throughout the template because the Principal Investigator of a cancer treatment trial is a physician. If this template is used for a trial where the Principal Investigator is not a physician, another appropriate term should be used instead of ‘study doctor’.
5. The template date in the header is for reference to this template only and should not be included in the informed consent form given to the prospective research participant.

**\*NOTES FOR LOCAL INVESTIGATORS:**

* The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs>/

1. A blank line, \_\_\_\_\_\_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
2. Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/>or call 1-800-4**-** CANCER (1-800-422-6237) to request a free copy.
3. Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

\*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

**Study Title**

**This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.**

**You are being asked to take part in this study because you have** *[Type/stage/presentation of cancer being studied is briefly described here. For example: “Colon cancer that has spread and has not responded to one treatment”.]* **and your liver does not function normally.**

**Why is this study being done?**

**The purpose of this study is to test the safety of** *[drug/intervention]* **at different dose levels in patients with cancer who have different degrees of abnormal liver function.**

*[Complete and include the following sentence if appropriate.]* **[***Agent name***] is an investigational or experimental anticancer agent that has not yet been approved by the Food and Drug Administration for use in patients with cancer who have livers that are not functioning normally.**

**How many people will take part in the study?**

**About** *[state total accrual goal here]* **people will take part in this study.** *[If appropriate, a short description about cohorts can be given here. For example: “At the beginning of the study, (enter number of first cohort) patients will be treated with a low dose of the drug. If this dose does not cause bad side effects, it will slowly be made higher as new patients take part in the study. A total of (enter maximum number) patients are the most that would be able to enter the study”.*

**What will happen if I take part in this research study?**

*[List tests and procedures and their frequency under the categories below. Include* *whether a patient will be at home, in the hospital, or in an outpatient setting.]*

**Before you begin the study …**

**You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.**

1. *[List tests and procedures as appropriate. Use bulleted format.]*

**During the study …**

**If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.**

1. *[List tests and procedures as appropriate. Use bulleted format.]*

**You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.**

1. *[List tests and procedures as appropriate. Use bulleted format. Omit this section if no tests or procedures are being done more often than usual.]*

**You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.**

1. *[List tests and procedures as appropriate. Use bulleted format. Omit this section if no tests or procedures are being tested in this study or required for safety monitoring.]*

*[For randomized studies:]* **You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an** *[equal/one in three/etc.]* **chance of being placed in any group.**

**If you are in group 1 (often called "Arm A") *…*** *[Explain what will happen for this group with clear indication of which interventions depart from routine care.]*

**If you are in group 2 (often called "Arm B")…** *[Explain what will happen for this group with clear indication of which interventions depart from routine care.]*

*[For studies with more than two groups, an explanatory paragraph containing the same type of information should be included for each group.]*

**When I am finished taking *[drugs or intervention]…****[Explain the follow-up tests, procedures, exams, etc. required, including the timing of each and whether they are part of standard cancer care or part of standard care but being performed more often than usual or being tested in this study. Define the length of follow-up.]*

*[Optional Feature: In addition to the mandatory narrative explanation found in the preceding text, a simplified calendar (study chart) or schema (study plan) may be inserted here. The schema from the protocol should not be used as it is too complex, however a simplified version of the schema is encouraged. Instructions for reading the calendar or schema should be included. See examples.]*

**Study Chart** *[Example]*

**You will receive** *[drug(s) or intervention]* **every** *[insert appropriate number of days or weeks]* **in this study. This** *[insert appropriate number of days or weeks]* **period of time is called a cycle. The cycle will be repeated** *[insert appropriate number]* **times. Each cycle is numbered in order. The chart below shows what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.**

**Cycle 1**

**Day What you do**

|  |  |  |
| --- | --- | --- |
| ­Two days before starting study | 1. Get routine blood tests. | |
| Day before starting study | 1. Check-in to \_\_\_\_\_\_\_\_\_\_\_\_\_ the evening before starting study. | |
| Day 1 | 1. Begin taking \_\_\_\_\_\_ once a day. Keep taking \_\_\_\_\_ until the end of study, unless told to stop by your health care team. | |
| Day 2 | 1. Leave \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ and go to where you are staying. | |
| Day 8 | 1. Get routine blood tests. | |
| Day 15 | 1. Get routine blood tests. | |
| Day 22 | 1. Get routine blood tests. | |
| Day 28 | 1. Get routine blood tests and exams. 2. Get 2nd chest x-ray for research purposes. | |
| Day 29 | 1. Return to your doctor’s office at \_\_\_\_\_\_\_ *[insert appointment time]* for your next exam and to begin the next cycle. |

**Future cycles**

**Day What you do**

|  |  |
| --- | --- |
| Days 1-28 | 1. Keep taking \_\_\_\_\_ once a day if you have no bad side effects and cancer is not getting worse. Call the doctor at \_\_\_\_\_\_\_\_\_\_\_\_\_ *[insert phone number]* if you do not know what to do. 2. Get routine blood tests each week (more if your doctor tells you to). 3. Get routine blood tests and exams every cycle (more if your doctor tells you to). 4. Get routine X-rays, CT scans, or MRIs every other cycle (more if your doctor tells you to). |
| Day 29 | 1. Return to your doctor’s office at \_\_\_\_\_\_\_ *[insert appointment time]* for your next exam and to begin the next cycle. |

**Study Plan** *[Example]*

**Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.**

#### Start Here

## Breast Cancer Surgery

### Medicines used in this study

### Doxorubicin + Cyclophosphamide by vein – given once every 21 days and repeated 4 times

### Randomize

(You will be inone Group or the other)

#### Group 2

### No Paclitaxel

#### Group 1

### Paclitaxel by vein

Every 21 days for 4 visits

**How long will I be in the study?**

**You will be asked to take** *[drugs or intervention]***for** *(months, weeks/until a certain event).* **After you are finished taking** *[drugs or intervention]*, **the study doctor will ask you to visit the office for follow-up exams for at least** *[indicate time frames and requirements of follow-up. When appropriate, state that the study will involve long-term follow-up and specify time frames and requirements of long-term follow-up. For example, “We would like to keep track of your medical condition for the rest of your life. We would like to do this by calling you on the telephone once a year to see how you are doing. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study.”]*

**Can I stop being in the study?**

**Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.**

**It is important to tell the study doctor if you are thinking about stopping so any risks from the** *[drugs or intervention]***can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.**

**The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.**

**What side effects or risks can I expect from being in the study?**

**You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the** *[drug(s) or intervention]***. In some cases, side effects can be serious, long lasting, or may never go away.** *[The next sentence should be included if appropriate.* **There also is a risk of death.***]*

**You should talk to your study doctor about any side effects that you have while taking part in the study.**

**Risks and side effects related to the** *[procedures, drugs, interventions, devices]* **include those which are:**

**Likely**



**Less Likely**



**Rare but serious**



*[Notes for consent form authors regarding the presentation of risks and side effects:*

* *Using a bulleted format, list risks and side effects related to the investigational aspects of the trial. Side effects of supportive medications should not be listed unless they are mandated by the study.*
* *List by regimen the physical and nonphysical risks and side effects of participating in the study in three categories: 1." likely"; 2. "less likely”; 3. “rare but serious".*
* *There is no standard definition of “likely" and "less likely”. As a guideline, “likely” can be viewed as occurring in greater than 20% of patients and “less likely” in less than or equal to 20% of patients. However, this categorization should be adapted to specific study agents by the principal investigator.*
* *In the “likely” and “less likely” categories, identify those side effects that may be ‘serious’. ‘Serious’ is defined as side effects that may require hospitalization or may be irreversible, long-term, life threatening or fatal.*
* *Side effects that occur in less than 2-3% of patients do not have to be listed unless they are serious, and should then appear in the “rare but serious” category.*
* *Physical and nonphysical risks and side effects should include such things as the inability to work. Whenever possible, describe side effects by how they make a patient feel, for example, “Loss of red blood cells, also called anemia, can cause tiredness, weakness and shortness of breath.”*
* *For some investigational drugs/interventions/devices there may be side effects that have been noted during treatment however not enough data is available to determine if the side effect is related to the drug/intervention/device. Because some local IRBs request to be informed of these possible side effects, this information, when available, is provided to the study chair. Inclusion of this information in the informed consent document is not mandatory. However, if included, these side effects should be listed under a separate category titled “Side effects reported by patients, but not proven to be caused by (drug/intervention/device)”. Side effects in this category do not have to be labeled as “likely”, “less likely” or “rare but serious” and should not be repeated here if they appear in a previous category. Similar to the other categories, these side effects should be listed in a bulleted format.]*

**Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.** *[Include a statement about possible sterility when appropriate. For example, “Some of the drugs used in the study may make you unable to have children in the future.” If appropriate include a statement that pregnancy testing may be required.]*

**For more information about risks and side effects, ask your study doctor.**

**Are there benefits to taking part in the study?**

**Taking part in this study may or may not make your health better. While doctors hope** *[procedures, drugs, interventions, devices]* **will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the safety of** *[procedures, drugs, interventions, devices]* **in patients with cancer who have abnormal liver function. This information could help future cancer patients.**

**What other choices do I have if I do not take part in this study?**

**Your other choices may include:**

* **Getting treatment or care for your cancer without being in a study**
* **Taking part in another study**
* **Getting no treatment**

*[Additional bullets should include, when appropriate, alternative specific procedures or treatments.]*

* *[For studies involving end-stage cancer, add the following paragraph as an additional bullet.]* **Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.**

**Talk to your doctor about your choices before you decide if you will take part in this study.**

**Will my medical information be kept private?**

**We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.**

**Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:**

* *[List relevant organizations like study sponsor(s), pharmaceutical company collaborators, local IRB, etc.]*
* **The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people**

**A description of this clinical trial will be available on** [**http://www.ClinicalTrials.gov**](http://www.ClinicalTrials.gov)**. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.**

*[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]*

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

**What are the costs of taking part in this study?**

**You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.**

*(If applicable, inform the patient of any tests or procedures for which there is no charge. Indicate if the patient and/or health plan is likely to be billed for any charges associated with these ‘free’ tests or procedures.)*

*(Include the following section if a study agent is manufactured by a drug company and provided at no charge)*

**The** *(identify study agent supplier here using the most appropriate choice of the following options: NCI, Cooperative Group, or another NCI-supported Clinical Trials Network)* **will supply the** *[study agent(s)]* **at no charge while you take part in this study. The** *(insert name of study agent supplier identified in first sentence)* **does not cover the cost of getting the** *[study agent(s)]* **ready and giving it to you, so you or your insurance company may have to pay for this.**

**Even though it probably won’t happen, it is possible that the manufacturer may not continue to provide the** *[study agent(s)]* **to the** *(insert name of study agent supplier identified in first sentence)* **for some reason. If this would occur, other possible options are:**

* **You might be able to get the** *[study agent(s)]* **from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.**
* **If there is no** *[study agent(s)]* **available at all, no one will be able to get more and the study would close.**

**If a problem with getting** *[study agent(s)]* **occurs, your study doctor will talk to you about these options.** *(End of section)*

*(Include the following section if a study agent is manufactured by the NCI and provided at no charge)*

**The NCI will provide the** *[study agent(s)]* **at no charge while you take part in this study. The NCI does not cover the cost of getting the** *[study agent(s)]* **ready and giving it to you, so you or your insurance company may have to pay for this.**

**Even though it probably won’t happen, it is possible that the NCI may not be able to continue to provide the** *[study agent(s)]* **for some reason. If this would happen, the study may have to close. Your study doctor will talk with you about this, if it happens.** *(End of section)*

**You will not be paid for taking part in this study.**

**For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at** [**http://cancer.gov/clinicaltrials/understanding/insurance-coverage**](http://cancer.gov/clinicaltrials/understanding/insurance-coverage) **. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.**

**Another way to get the information is to call 1-800-4**-**CANCER (1-800-422-6237) and ask them to send you a free copy.**

**What happens if I am injured because I took part in this study?**

**It is important that you tell your study doctor, \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** *[investigator’s name(s)],* **if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** *[telephone number].*

**You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.**

**What are my rights if I take part in this study?**

**Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.**

**We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.**

**In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.**

**Who can answer my questions about the study?**

**You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** *[name(s)]* **at \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** *[telephone number].*

**For questions about your rights while taking part in this study, call the \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** *[name of center]* **Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

**\*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).** *[\*Only applies to sites using the CIRB.]*

**Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.**

**You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.**

*[Insert information about companion studies here. Provide yes/no options at each decision point. The following studies are included as examples therefore are written with italicized font. Any text provided for patients should use the same non-italicized font as used for the rest of the informed consent document.]*

*[Example: Quality of Life study]*

*Quality of Life Study*

*We want to know your view of how your life has been affected by cancer and its treatment. This “Quality of life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.*

*This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer*.

*You will be asked to complete 3 questionnaires: one on your first visit, one 6 months later, and the last one 12 months after your first visit. It takes about 15 minutes to fill out each questionnaire.*

*If any questions make you feel uncomfortable, you may skip those questions and not give an answer.*

*If you decide to take part in this study, the only thing you will be asked to do is fill out the three questionnaires. You may change your mind about completing the questionnaires at any time.*

*Just like in the main study, we will do our best to make sure that your personal information will be kept private.*

*Please circle your answer.*

*I choose to take part in the Quality of Life Study. I agree to fill out the three Quality of Life Questionnaires.*

*YES NO*

*[Example: Use of Tissue for Research]*

*[The following example of tissue consent has been taken from the NCI Cancer Diagnosis Program’s model tissue consent form found at the following URL:*

<http://www.cancerdiagnosis.nci.nih.gov/humanSpecimens/ethical_collection/model.pdf>  ***]***

*Consent Form for Use of Tissue for Research*

***About Using Tissue for Research***

*You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.*

*We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research.*

*Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.*

*Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.*

***Things to Think About***

*The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care.*

*If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.*

*In the future, people who do research may need to know more about your health. While the xyz may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.*

*Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.*

*Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.*

***Benefits***

*The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.*

***Risks***

*The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.*

***Making Your Choice***

*Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.*

*No matter what you decide to do, it will not affect your care.*

*1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.*

|  |  |
| --- | --- |
| *Yes* | *No* |

*2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).*

|  |  |
| --- | --- |
| *Yes* | *No* |

*3. Someone may contact me in the future to ask me to take part in more research.*

|  |  |
| --- | --- |
| *Yes* | *No* |

**Where can I get more information?**

**You may call the National Cancer Institute's Cancer Information Service at:**

**1-800-4-CANCER (1-800-422-6237)**

**You may also visit the NCI Web site at** [**http://cancer.gov/**](http://cancer.gov/)

* **For NCI’s clinical trials information, go to:** [**http://cancer.gov/clinicaltrials/**](http://cancer.gov/clinicaltrials/)
* **For NCI’s general information about cancer, go to** [**http://cancer.gov/cancerinfo/**](http://cancer.gov/cancerinfo/)

**You will get a copy of this form. If you want more information about this study, ask your study doctor.**

**Signature**

**I have been given a copy of all \_\_\_\_\_** *[insert total of number of pages]* **pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

**Participant \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

APPENDIX A

**Child-Pugh Classification (CPC) of liver dysfunction**

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** | **Unrousable 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.

APPENDIX B

**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 C**

**CTEP MULTICENTER GUIDELINES**

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines 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 D**

**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
* creatinine level within normal institutional limits

OR

* creatinine clearance >60 mL/min/1.73 m2 if patient’s creatinine level is above institutional 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 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**

Total bilirubin □ < ULN□ >1.0-1.5x ULN□ >1.5x – 3x ULN□ >3x ULN

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

(mm/dd/yyyy)

SGOT/AST □ < ULN□ > ULN

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

(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, Last Name

MM DD YYYY Person Completing Form, First Name

Date Informed Consent Signed Person Completing Form, Phone (\_\_\_\_)

MM DD YYYY Person Completing Form, Fax (\_\_\_\_)

Projected Start Date of Treatment Person Completing Form, E-mail

MM DD YYYY

Date of Registration

MM DD YYYY

**Patient Demographics / Pre-Treatment Characteristics**

Patient Name, Last Patient Name, First Patient Name, 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 & Medicare* 🞎 *No means of payment*

*(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 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