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# An Innovative Phase I Trial Design Allowing for the Identification of Multiple Potential Maximum Tolerated Doses with Combination Therapy of Targeted Agents

Sarina A. Piha-Paul

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By

Sarina A. Piha-Paul, B.S., M.D.

APPROVED:

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Razelle Kurzrock, M.D.
Supervisory Professor

_____

Jonathan Trent, M.D., Ph.D.

_____

David Hong, M.D.

_____

Donald Berry, Ph.D.

_____

Karin Hahn, M.D.

APPROVED:

_____

Dean, the University of Texas
Graduate School of Biomedical Sciences at Houston

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A

THESIS

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and
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for the Degree of

MASTER OF SCIENCE

By

Sarina Anne Piha-Paul, B.S., M.D.
Houston, Texas

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# An Innovative Phase I Trial Design Allowing for the Identification of Multiple Potential Maximum Tolerated Doses with Combination Therapy of Targeted Agents

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Sarina A. Piha-Paul, MD

Supervisory Professor: Razelle Kurzrock, MD

**Abstract**

Treatment for cancer often involves combination therapies used both in medical practice and clinical trials. Korn and Simon listed three reasons for the utility of combinations: 1) biochemical synergism, 2) differential susceptibility of tumor cells to different agents, and 3) higher achievable dose intensity by exploiting non-overlapping toxicities to the host. Even if the toxicity profile of each agent of a given combination is known, the toxicity profile of the agents used in combination must be established. Thus, caution is required when designing and evaluating trials with combination therapies. Traditional clinical design is based on the consideration of a single drug. However, a trial of drugs in combination requires a dose-selection procedure that is vastly different than that needed for a single-drug trial.

When two drugs are combined in a phase I trial, an important trial objective is to determine the maximum tolerated dose (MTD). The MTD is defined as the dose level below the dose at which two of six patients experience drug-related dose-limiting toxicity (DLT). In phase I trials that combine two agents, more than one MTD generally exists, although all are rarely determined. For example, there may be an MTD that includes high doses of drug A with lower doses of drug B, another one for high doses of drug B with lower doses of drug A, and yet another for intermediate doses of both drugs administered together. With classic phase I trial

designs, only one MTD is identified. Our new trial design allows identification of more than one MTD efficiently, within the context of a single protocol.

The two drugs combined in our phase I trial are temsirolimus and bevacizumab. Bevacizumab is a monoclonal antibody targeting the vascular endothelial growth factor (VEGF) pathway which is fundamental for tumor growth and metastasis. One mechanism of tumor resistance to antiangiogenic therapy is upregulation of hypoxia inducible factor 1α (HIF-1α) which mediates responses to hypoxic conditions. Temsirolimus has resulted in reduced levels of HIF-1α making this an ideal combination therapy.

Dr. Donald Berry developed a trial design schema for evaluating low, intermediate and high dose levels of two drugs given in combination as illustrated in a recently published paper in Biometrics entitled "A Parallel Phase I/II Clinical Trial Design for Combination Therapies." His trial design utilized cytotoxic chemotherapy. We adapted this design schema by incorporating greater numbers of dose levels for each drug. Additional dose levels are being examined because it has been the experience of phase I trials that targeted agents, when given in combination, are often effective at dosing levels lower than the FDA-approved dose of said drugs. A total of thirteen dose levels including representative high, intermediate and low dose levels of temsirolimus with representative high, intermediate, and low dose levels of bevacizumab will be evaluated.

We hypothesize that our new trial design will facilitate identification of more than one MTD, if they exist, efficiently and within the context of a single protocol. Doses gleaned from this approach could potentially allow for a more personalized approach in dose selection from among the MTDs obtained that can be based upon a patient's specific co-morbid conditions or anticipated toxicities.

# Table of Contents

# List of Illustrations

# List of Tables

# List of Abbrevations

| | |
|---|---|
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| Beta HCG | Beta Human Chorionic Gonadotropin |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CLIA | Clinical Laboratory Improvement Amendments |
| CNS | Central Nervous System |
| CR | Complete Remission/Complete Response |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| DCE-MRI | Dynamic Contrast-Enhanced Magnetic Resonance Imaging |
| DLT | Dose-Limiting Toxicity |
| ECOG | Eastern Cooperative Oncology Group |
| EKG | Electrocardiogram |
| FDA | Food and Drug Administration |
| FLT-1 | FMS-Like Tyrosine |
| HER-2 | Human Epidermal Growth Factor Receptor-2 |
| HIF-1a | Hypoxia Inducible Factor-1-Alpha |
| ICH | Immunohistochemistry |
| IGFR | Insulin Growth Factor Receptor |
| IRB | Institutional Board Review |
| IULN | Institutional Upper Limit of Normal |

| | |
|---|---|
| IV | Intravenously |
| KDR | Kinase Insert Domain Receptor |
| LD | Longest Diameter |
| mRNA | Messenger Ribonucleic Acid |
| MTD | Maximum Tolerated Dose |
| mTOR | Mammalian Target of Rapamycin |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NSCLC | Non-Small Cell Lung Cancer |
| ORE&RM | Office of Research Education and Regulatory Management |
| PD | Progressive Disease |
| PI3 kinase | Phosphatidylinositol 3-kinase |
| PT | Prothrombin Time |
| PTEN | Phosphatase and Tensin Homolog |
| PTT | Partial Thromboplastin Time |
| PR | Partial Remission/Partial Response |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| VEGF | Vascular Endothelial Growth Factor |

# PART I

# Background

## Anticancer Drug Development

Anticancer drug development adheres to an orderly and patterned process. Preclinical data are collected, including information on efficacy, toxicology data, and mechanism(s) of action. If a new drug in the preclinical setting shows promise, meaning that there is a reasonable expectation of safety and benefit to the patient, the drug will move forward in testing in three separate phases. Phase I testing is performed to establish a recommended dose and schedule for phase II testing. The recommended dose is based on observed toxic effects and pharmacokinetic outcomes. Phase II testing is conducted to determine whether the drug shows any evidence of activity in a specific tumor type or subtype within a given tumor type. Finally, the goal of phase III testing is to elucidate whether the new drug, alone or in combination, produces a meaningful response, as determined by increased overall survival, increased time to tumor progression, increased progression-free survival and/or other quality of life parameters. It is important to note, however, that these separate phases are not mutually exclusive in that phase I testing seeks preliminary evidence of antitumor activity, whereas phase II and III testing continually reassesses drug safety and tolerability.

Anticancer drug development began in the 1960s with cytotoxic chemotherapy. The impetus during this time period was to define the maximum tolerated dose (MTD) as when the toxic effects of the drug, mainly myelosuppression, proved the desired effects of the new drug on the tumor (2-4). However, over the past several decades, we have seen the emergence of rationally designed agents that target molecular pathways via intracellular and/or extracellular targets thought to be relevant to malignant transformation or development of metastases, with the additional objective of sparing noncancerous cells. In this era of targeted therapy, many questions arise regarding the relevance of the "old" method of establishing the recommended

dose and schedule as the newer agents frequently do not produce traditional toxic effects, might not be directly cytotoxic, and ideally, produced effects only on defined subtypes within a specific tumor type. Elizabeth Eisenhauer in "Phase I Cancer Clinical Trials: A Practical Guide" asks the vital questions: 1) Is dosing to toxicity appropriate or necessary? and, 2) Can direct measures of target effect be utilized to determine dose(4)? Regardless of the many questions that have arisen as to how best to proceed with phase I testing of newly developed targeted therapeutic agents, the fact remains that phase I trials are the gateway to drug development and approval.

## Phase I Trial Design

Phase I trials generally have a small sample size and are nonrandomized, dose escalation studies. For most trials, the endpoint is dose-limiting toxicity (DLT). The range of doses to be evaluated is generally established on the basis of preclinical data. The human starting dose of the drug in phase I testing is usually one-tenth of the lethal dose in 10% of animals [LD10]. The mouse toxic dose equivalent is typically used. However, if other animal species show more toxicity, one-third to one-sixth of the lowest toxic dose equivalent is used from the most sensitive species.

The MTD is usually defined as the dose at which one-third of patients experience a DLT. The recommended phase II dose is usually defined as the dose level just below the dose at which DLTs were observed in at least one-third of patients. However, the MTD may be determined using the additional variables of drug cost, drug availability, and-or drug delivery issues.

Dose escalation typically proceeds using a modified Fibonacci series, whereby the relative increase between successive dose levels is constant, e.g., 2.00, 1.67, 1.50, 1.40, 1.33,

1.33, etc. The classical phase I trial design is a "3 + 3" design whereby three patients are enrolled on the first dose level. If zero of three patients experience a DLT, three patients are then enrolled on the next dose level. If two of three patients experience DLT, dose escalation will stop. Three additional patients will then be enrolled on the next lowest dose level if only three patients were treated previously at that dose. If one of three patients experiences a DLT, three more patients are enrolled. Of those three additional patients, if none experience DLT, dose escalation will proceed; if one or more of this group suffers DLT, dose escalation will stop and the next lowest dose level is declared the MTD; and if two or more of this group experience DLT, dose escalation is stopped and three additional patients are enrolled on the next lowest dose level if only three patients were treated previously at that dose.

## Combination Therapy in Cancer Treatment

Treatment for cancer often involves combination therapies used both in medical practice and clinical trials. Korn and Simon listed three reasons for the utility of combinations: 1) biochemical synergism, 2) differential susceptibility of tumor cells to different agents, and 3) higher achievable dose intensity by exploiting non-overlapping toxicities to the host(5). Even if the toxicity profile of each agent of a given combination is known, the toxicity profile of the agents used in combination must be established. Thus, caution is required when designing and evaluating trials with combination therapies. Traditional clinical design is based on the consideration of a single drug. However, a trial of drugs in combination requires a dose-selection procedure that is vastly different than that needed for a single-drug trial.

When two drugs are combined in a phase I trial, an important trial objective is to determine the MTD and DLTs of the combination. In phase I trials that combine two agents, more than one

MTD generally exists, although all are rarely determined. For example, there may be an MTD that includes high doses of drug A with lower doses of drug B, another one for high doses of drug B with lower doses of drug A, and yet another for intermediate doses of both drugs administered together. With classic phase I trial designs, only one MTD is identified.

## Angiogenesis and Bevacizumab

Growing tumors receive nutrients, growth factors, oxygen, proteolytic enzymes, hemolytic factors, and hormones through the process of angiogenesis, which plays a key role in metastatic pathogenesis (6-8). The vascular endothelial growth factor (VEGF) family of proteins and receptors are important in tumor angiogenesis and are fundamental for tumor growth and metastasis (9, 10). Bevacizumab is a monoclonal antibody specific for VEGF. Bevacizumab binds to human VEGF and prevents interaction of VEGF with its receptors, FMS-like tyrosine kinase 1 (Flt-1) and kinase insert domain receptor (KDR) on the surface of endothelial cells (11). Bevacizumab works by inhibiting angiogenesis and thus may reduce microvascular growth of tumors and inhibit metastatic disease progression (11-13).

Bevacizumab is administered intravenously (IV). Bevacizumab is United States Food and Drug Administration (FDA) approved for use in combination IV fluorouracil-based chemotherapy as the first-line or second-line treatment for metastatic colon or rectal cancer at 5 mg/kg or 10 mg/kg every 14 days. Bevacizumab also has FDA approval in combination with carboplatin and paclitaxel for the first-line treatment of unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer (NSCLC) at 15 mg/kg every 21 days and in combination with paclitaxel chemotherapy for the first-line treatment of advanced human epidermal growth factor receptor-2 (HER-2) negative breast cancer at 10 mg/kg every two

weeks. Finally, bevacizumab has FDA approval in metastatic renal cell carcinoma at 10 mg/kg every 14 days in combination with interferon alpha and in glioblastoma multiforme for patients who have progressed on prior therapy as a single agent at 10 mg/kg every 14 days.

## Resistance to Antiangiogeneic Therapy

Because diverse receptors in signaling networks communicate with each other via cross-talk, tumor growth and survival are regulated by various receptors and signaling pathways, not merely by one receptor or a single signaling pathway (14, 15). Tumors often become resistant to antiangiogenic therapy. One mechanism for such resistance is upregulation of HIF-1 α. When HIF-1α is upregulated, adaptive responses to hypoxic conditions are modulated through its over-expression, increasing levels of VEGF and subsequent aggressive tumor growth and infelicitous patient outcomes (8, 12, 16-26).

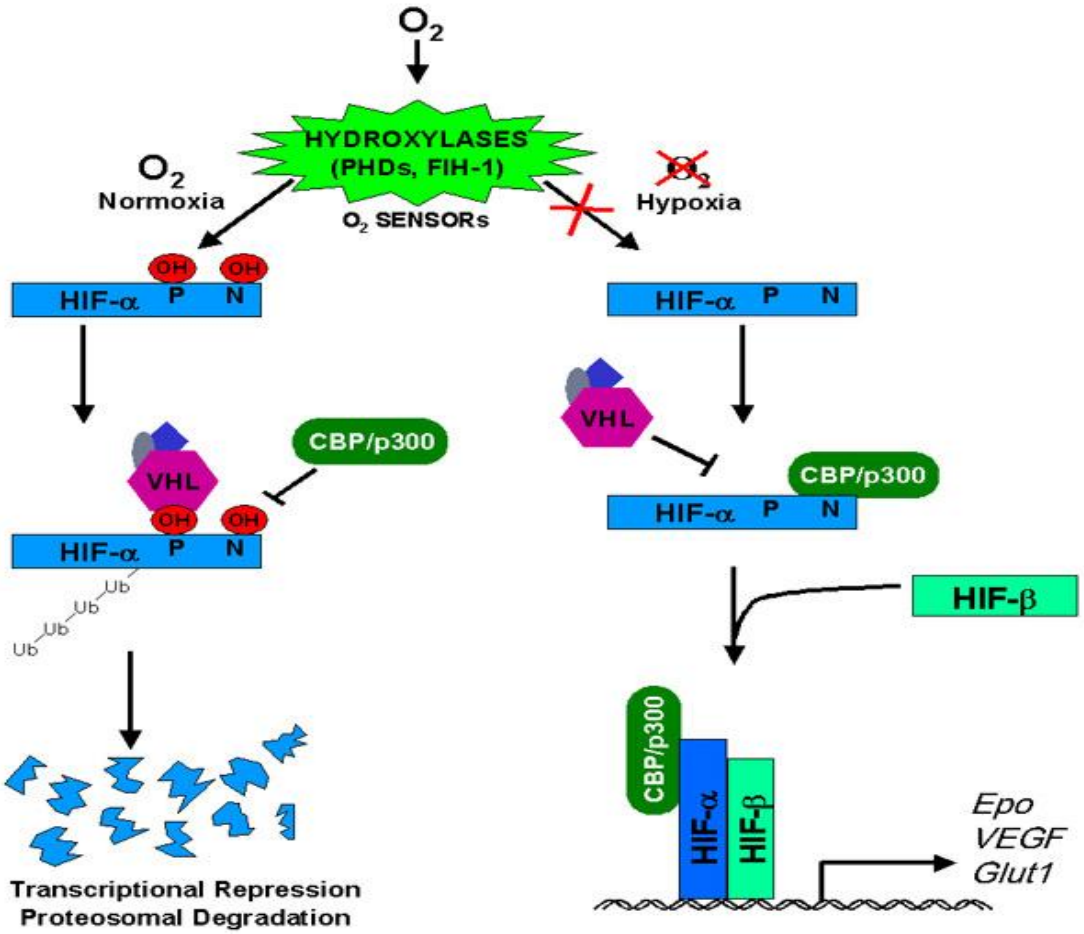


**Figure 1: HIF-1α Pathway.**
Used with permission from Dr. Daniel Peet, Senior Lecturer.
School of Molecular and Biomedical Science, University of Adelaide, Australia.
CRICOS Provider Number 00123M
http://www.adelaide.edu.au/mbs/research/peet/

## Temsirolimus as an Inhibitor of HIF-1

Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine/threonine kinase involved in the initiation of messenger ribonucleic acid (mRNA) translation (27, 28). *In vitro* studies with temsirolimus in renal cell carcinoma cell lines demonstrated inhibition of mTOR activity, and resulted in reduced levels of HIF-1α, HIF-2α and VEGF (29). Also, in the HER-2 gene amplified breast cancer cell line BT474, temsirolimus inhibited VEGF production in vitro under both normoxic and hypoxic conditions through inhibition of HIF-1 expression and

transcriptional activation (30). Temsirolimus is administered IV and is FDA-approved as a first-line therapy in patients with advanced renal cell carcinoma who had 3 or more of 6 poor prognostic factors at 25 mg IV given weekly (31).

## Rationale for Combining Bevacizumab and Temsirolimus

Temsirolimus inhibits HIF-1α, which abrogates its ability to render cancer cells resistant to antiangiogenic therapy. Thus, temsirolimus is an excellent agent for combination with bevacizumab. Furthermore, bevacizumab and temsirolimus as single agents have observed common toxicities that are non-overlapping. Nonetheless, we plan to monitor patients very closely during the first cycle of combination therapy to evaluate safety and tolerability. We also plan to establish the appropriate dose for phase II efficacy studies and provide preliminary data on antitumor activity.

## Novel Phase I Trial Design

Dr. Donald Berry developed a trial design schema allowing for evaluating low, intermediate and high dose levels of two drugs given in combination as illustrated in a recently published paper in Biometrics entitled "A Parallel Phase I/II Clinical Trial Design for Combination Therapies.(32)" His trial design utilized cytotoxic chemotherapy. We adapted this design schema by incorporating greater numbers of dose levels for each drug. Additional dose levels are being examined because it has been the experience of phase I trials that targeted agents, when given in combination, are often effective at dosing levels lower than the FDA-approved dose of said drugs.

A total of thirteen dose levels including representative high, intermediate and low dose levels of temsirolimus with representative high, intermediate, and low dose levels of

bevacizumab will be evaluated. This will allow us to identify multiple potential MTDs of each drug given in combination. We are excited by this trial design as the classic phase I design would take three separate trials to determine this.

We hypothesize that our new trial design will facilitate identification of more than one MTD, if they exist because the maximum dose of each drug is not tolerable in combination, efficiently and within the context of a single protocol. Doses gleaned from this approach could potentially lead to a personalized approach in dose selection from among the MTDs obtained that can be based upon a patient's specific co-morbid conditions or anticipated toxicities.

# PART II

# Clinical Trial Design:
# A Phase I Trial of Bevacizumab and Temsirolimus in Patients with Advanced Malignancies

## Objectives

Primary Objective

To determine the maximum tolerated doses (MTDs) and dose-limiting toxicities (DLTs) of combination treatment with bevacizumab and temsirolimus.

Secondary Objectives

- Preliminary descriptive assessment of antitumor efficacy.
- Assessment of antiangiogenesis correlates.

## Timeline

The clinical trial of bevacizumab and temsirolimus in patients with advanced malignancies was approved by the M. D. Anderson Cancer Center Institutional Board Review (IRB) on October 25, 2007, and was activated at M. D. Anderson Cancer Center on January 25, 2008. The trial began patient accrual in February 2008.

We estimate that the number of patients required to find the MTDs of this drug combination and to obtain adequate correlative studies is approximately 50-60 patients. The allowable number of patients that **can** be enrolled on the trial, given 13 total dose levels, is 78 patients (if six patients are enrolled at each dose level). Also, predicting that we may discover 3-4 potential MTDs and allowing for expansion of 10 additional patients at those MTDs, we expect an absolute **maximum of 118 patients for the trial**. However, it is important to note that we do not predict that all 13 dose levels will be explored due to some dosing levels being closed secondary to discovery of a DLT. The estimated accrual rate is 1 - 5 patients per month. All patients will be followed for 30 days after discontinuation of the study or after withdrawal from the study.

## Rationale for Selected Dose and Schedule of Bevacizumab and Temsirolimus

We have designed this clinical trial combining bevacizumab and temsirolimus in patients with advanced malignancies on the basis of the following principles:

1. Multiple dose levels of each drug are being examined because it has been the phase I trial experience that targeted agents, when given in combination, are often effective at dosing levels lower than the FDA-approved dose of said drugs.
2. The HIF-1α inhibition properties of temsirolimus make it an excellent agent for combination with bevacizumab in an effort to overcome resistance to antiangiogenic therapy.
3. These two targeted agents have mostly non-overlapping toxicities and might be amenable to escalation to full doses in combination.

Bevacizumab is a recombinant, humanized, monoclonal antibody specific for VEGF(11). Bevacizumab binds to human VEGF and prevents interaction of VEGF with its receptors, Flt-1 and KDR, on the surface of endothelial cells(11). Bevacizumab is administered intravenously (IV). Bevacizumab is United States Food and Drug Administration (FDA) approved for use in combination intravenous fluorouracil-based chemotherapy as a first-line or second-line treatment of metastatic colon or rectal cancer at 5 mg/kg or 10 mg/kg every 14 days. Bevacizumab also has FDA approval in combination with carboplatin and paclitaxel for the first-line treatment of unresectable, locally advanced, recurrent or metastatic, non-squamous, non-small cell lung cancer (NSCLC) at 15 mg/kg every 21 days and in combination with paclitaxel chemotherapy for the first-line treatment of advanced human epidermal growth factor receptor-2 (HER-2) negative breast cancer at 10 mg/kg every two weeks. Finally, bevacizumab has FDA approval in

metastatic renal cell carcinoma at 10 mg/kg every 14 days in combination with interferon alpha and in glioblastoma multiforme as a single agent for patients who have progressed on prior therapy as a single agent at 10 mg/kg every 14 days. Based on these dosing schedules, we have decided to explore dosing levels ranging from 2.5 mg/kg to 15 mg/kg every 21 days.

Temsirolimus [sirolimus 42-ester with 2,2-bis(hydroxymethyl) propionic-acid], an ester of the macrocyclic immunosuppressive agent sirolimus (rapamycin, Rapamune™), is a cytostatic cell cycle inhibitor with antitumor properties. Temsirolimus inhibits mTOR, a serine/threonine kinase involved in the initiation of mRNA translation(27, 28). Temsirolimus is administered IV. Temsirolimus is FDA-approved as a first-line therapy in patients with advanced renal cell carcinoma who had 3 or more of 6 poor prognostic factors at 25 mg IV given weekly(31). On the basis of this dosing schedule, we have decided to explore dosing levels ranging from 5 mg to 25 mg on days 1, 8, and 15 of a 21-day cycle.

At the above doses of bevacizumab and temsirolimus, observed common toxicities of each single agent are non-overlapping. Nonetheless, we plan to monitor patients very closely with weekly labs and toxicity checks during the first cycle of combination therapy.

## Patient Selection

"Inclusion Criteria

1) Patients with advanced or metastatic cancer that is refractory to standard therapy, relapsed after standard therapy, or who have no standard therapy that induces a complete response (CR) rate of at least 10% or improves survival by at least three months.
2) Patients should be at least four weeks from the last day of therapeutic radiation or cytotoxic chemotherapy or from antibody therapy, or at least five half-lives from non-cytotoxic targeted or biologic therapy.
3) Eastern Cooperative Oncology Group (ECOG) performance status </= 2 (Karnofsky >/= 60%). See Appendix 1.
4) Patients must have allowable organ and marrow function defined as:
    - absolute neutrophil count >/= 1,000/µL
    - platelets >/= 75,000/µL

- creatinine </= 3 X Institutional Upper Limit of Normal (IULN)
- total bilirubin </= 3.0 mg/dL
- AST(SGOT)/ALT(SGPT) </= 5 X IULN
- fasting level of total cholesterol of no more than 350 mg/dL
- triglyceride level of no more than 400 mg/dL

5) Temsirolimus is a Pregnancy Category D drug. For this reason and because chemotherapeutic agents are known to be teratogenic, women of child-bearing potential (defined as women who are not post-menopausal for 12 months or who have had no previous surgical sterilization) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days after the last dose. Should a women become pregnant or suspect she is pregnant while participating on this study, she should inform her treating physician immediately.
6) Female patients of childbearing potential should have a normal plasma beta human chorionic gonadotropin (beta HCG).
7) Ability to understand and the willingness to sign a written informed consent document.
8) Patients may not be receiving any other investigational agents and/or any other concurrent anticancer agents or therapies.

Exclusion Criteria

1) Patients with hemoptysis within 28 days prior to entering the study.
2) Patients with clinically significant unexplained bleeding within 28 days prior toentering the study.
3) Uncontrolled systemic vascular hypertension (systolic blood pressure > 140 Mm Hg, diastolic blood pressure > 90 mm Hg on medication).
4) Patients with clinically significant cardiovascular disease:
   - History of CVA within 6 months
   - Myocardial infarction or unstable angina within 6 months
   - Unstable angina pectoris
5) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics on Day 1.
6) Pregnant or breastfeeding women. Temsirolimus is Pregnancy Category D.
7) History of hypersensitivity to bevacizumab, murine products, or any component of the formulation.
8) History of hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or to any component of the formulation.
9) Patients who are taking CYP3A4 inducers and/or inhibitors. If a patient has a history of taking CYP3A4 inducers and/or inhibitors prior to enrollment on protocol, a patient must wait at least 5 half-lives of said drug before initiating therapy on protocol.
10) Patients with primary central nervous system (CNS) tumor or CNS metastases by head CT or MRI."(33)

Several changes were made to the above eligibility criteria after the information was posted on the website. These changes are listed below:

- Removed the exclusion criteria:

  6) Patients with primary central nervous system (CNS) tumor or CNS metastases by head CT or MRI.

- Modified in the exclusion criteria:

  4) Patients must have allowable organ and marrow function defined as platelets >/= 50,000/µL

- Removed the exclusion criteria:

  5) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics on Day 1.

- Modified in the inclusion criteria:

  2) Patients may have received palliative radiation immediately before (or during) treatment provided radiation is not to the only target lesion available.

- Modified in the inclusion criteria:

  If a patient has a history of taking CYP3A4 inducers and/or inhibitors prior to enrollment on protocol, **it is strongly recommended that the** patient **stops the drug** and waits at least 5 half-lives of said drug before initiating therapy on protocol.

# Treatment Plan

Pretreatment Evaluation

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, all patients will undergo rigorous evaluation and testing prior to the initiation of treatment, including the following:

1) Complete history and physical examination, including documentation of all measurable disease as well as signs, symptoms, concurrent medications, and performance status.

2) Laboratory studies: Complete blood count (CBC) with differential, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, aspartate aminotransferase (SGOT[AST]), alanine aminotransferase (SGPT[ALT]), prothrombin time /partial thromboplastin time (PT/PTT), fasting serum total cholesterol, fasting triglyceride level, urinalysis, serum pregnancy test (women of childbearing potential).

3) 12-lead electrocardiogram (EKG) within 28 days prior to starting treatment.

4) Radiologic evaluation of measurable disease and pertinent tumor markers within 4 weeks before starting treatment. If the patient does not have radiologically measurable disease but has cutaneously measurable disease, this must be documented at the pretreatment evaluation physical examination (34).

Treatment

Treatment will be administered on an outpatient basis. Both bevacizumab and temsirolimus infusions will be given at M. D. Anderson Cancer Center. A cycle of therapy consists of 21 days. No investigational or commercial agents or therapies other than those described here may be administered with the intent to treat the patient's malignancy.

Temsirolimus

Temsirolimus will be given with bevacizumab on Day 1 of each cycle. Temsirolimus will be given as a single agent on Days 8 and 15 of each cycle. Temsirolimus infusions will be administered at the patient cohort dosing level IV over 60 minutes for the first cycle and over 30 minutes for subsequent cycles if the patient tolerates the first infusion well.

Bevacizumab

Bevacizumab will be given on Day 1 only of each cycle. Bevacizumab infusions will be administered at the patient cohort dosing level IV over 90 minutes for the first cycle and over 60 minutes for subsequent cycles if the patient tolerates the first infusion well.

Trial Design

We adapted Dr. Donald Berry's trial design schema (see Figure 2) as illustrated in a recently published paper in Biometrics entitled "A Parallel Phase I/II Clinical Trial Design for Combination Therapies" to allow for exploration of a greater number of dose levels. In doing this, we will be able to efficiently explore representative high, intermediate and low dose levels of temsirolimus with representative high, intermediate

and low dose levels of bevacizumab within the context of this one protocol. Dose levels are found in Table 1. Figure 3 is a visual representation of our modified design schema. Whenever a dose level is determined to be above the MTD, all dose levels to the right of and above the vertical dotted line are no longer permissible as they would be expected to also be above the MTD. For instance, if dose level 3 is above the MTD because of DLTs at that dose level, then dose levels 6, 9, and 13 would be expected to be above the MTD and would no longer be permissible (and would not be explored).

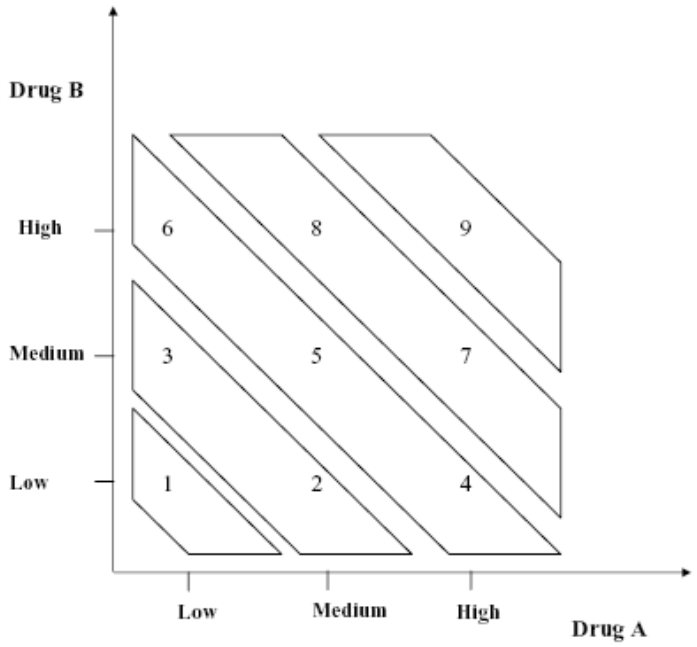


**Figure 2: An Illustration of Combination Doses.**
Used with permission from Dr. Donald Berry
Division Head, Quantitative Sciences Division
The University of Texas MD Anderson Cancer Center

## TABLE 1: Dose-Escalation Schedule

| Dose Level | Dose and Schedule (21-day cycle) | |
|---|---|---|
| | **Temsirolimus** | **Bevacizumab** |
| Level 1 | 5 mg days 1, 8, and 15 every 21 days | 5 mg/kg day 1 every 21 days |
| Level 2 | 5 mg days 1, 8, and 15 every 21 days | 10 mg/kg day 1 every 21 days |
| Level 3 | 5 mg days 1, 8, and 15 every 21 days | 15 mg/kg day 1 every 21 days |
| Level 4 | 12.5 mg days 1, 8, and 15 every 21 days | 2.5 mg/kg day 1 every 21 days |
| Level 5 | 12.5 mg days 1, 8, and 15 every 21 days | 7.5 mg/kg day 1 every 21 days |
| Level 6 | 12.5 mg days 1, 8, and 15 every 21 days | 15 mg/kg day 1 every 21 days |
| Level 7 | 20 mg days 1, 8, and 15 every 21 days | 2.5 mg/kg day 1 every 21 days |
| Level 8 | 20mg days 1, 8, and 15 every 21 days | 7.5 mg/kg day 1 every 21 days |
| Level 9 | 20 mg days 1, 8, and 15 every 21 days | 15 mg/kg day 1 every 21 days |
| Level 10 | 25 mg days 1, 8, and 15 every 21 days | 2.5 mg/kg day 1 every 21 days |
| Level 11 | 25 mg days 1, 8, and 15 every 21 days | 5 mg/kg day 1 every 21 days |
| Level 12 | 25 mg days 1, 8, and 15 every 21 days | 10 mg/kg day 1 every 21 days |
| Level 13 | 25 mg days 1, 8, and 15 every 21 days | 15 mg/kg day 1 every 21 days |

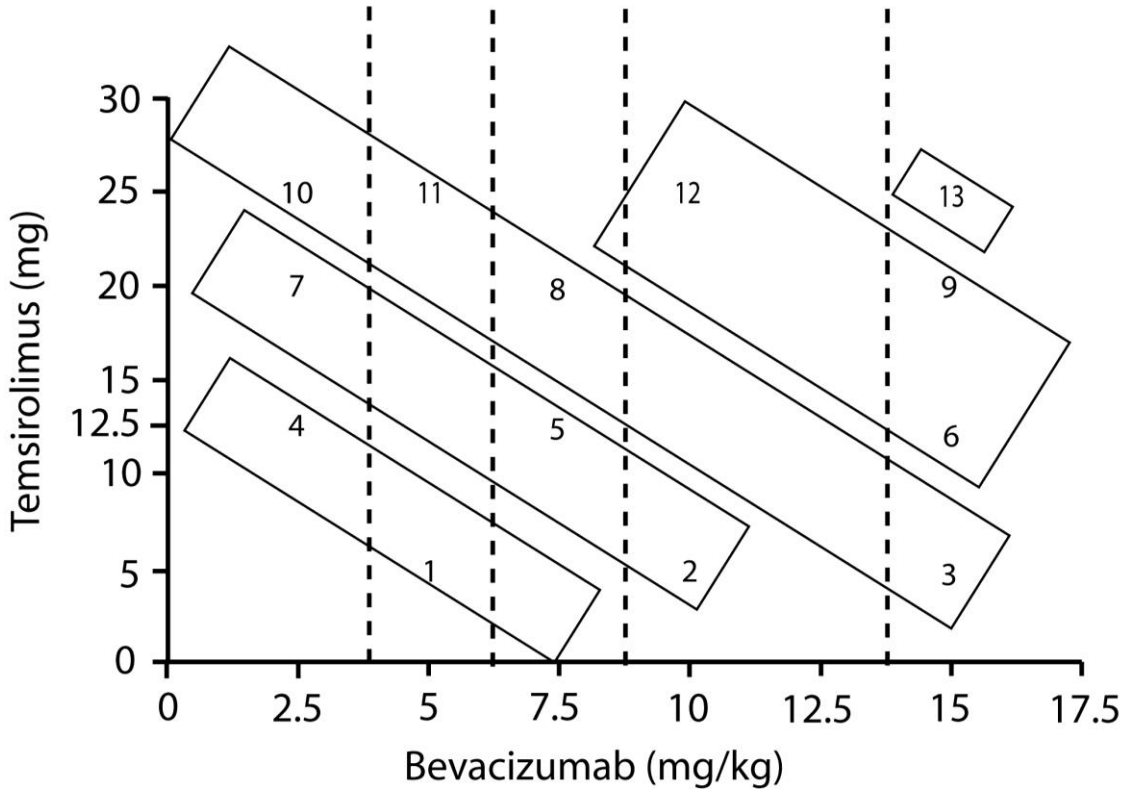


**Figure 3: Treatment Plan: Modified Design Schema**

This protocol will utilize a Phase I escalation design (see Table 2) with three to four patients per cohort in an effort to obtain three evaluable patients. Three to four patients will be entered at each dose level in order to obtain adequate correlative data in addition to the safety data. Three to four patients will be treated at dose level 1 and evaluated for toxicity. Dose escalation will then proceed as follows:

**Table 2: Dose Escalation Design**

| Number of Patients with DLT at a Given Dose Level | Escalation Decision Rule |
|---|---|
| 0 out of 3 | Enter 3 patients at the next dose level. |
| $\geq$2 out of 3 | Dose escalation will be stopped. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. |
| 1 out of 3 | Enter at least 3 more patients at this dose level.<br>• If 0 of these 3 patients experience DLT, proceed to the next dose level.<br>• If 1 or more of this group suffer DLT, then dose escalation is stopped, and next lowest dose is declared as a maximum tolerated dose (MTD).<br>• If 2 or more of this group suffer DLT, then dose escalation is stopped. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. |

Modified from Cancer Therapy Evaluation Program (CTEP) website(1). See Appendix 4.

Because of the specific design of this trial, more than one potential MTD may be identified. As is standard for investigator initiated protocols in the Department Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, the MTDs identified will be expanded by up to 10 additional patients to further evaluate toxicity and correlative data (34).

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, up to three additional patients will be permitted to be added to a cohort for evaluation of safety and/or correlative studies. These

patients will be considered in the DLT analysis. If a response is observed in a particular tumor type with the study drug combination, enrollment will be permitted to be expanded to include a total of 14 patients with that tumor type. All enrolled participants of that tumor type will be considered in the DLT analysis. If at any time more than or equal to one-third of the participants at a dose level experience a DLT, that dose will be considered to be above the MTD, and the dose of the study drugs will be de-escalated. A tumor response will be defined as one or more of the following: 1) stable disease for more than or equal to four months, 2) decrease in the sum of target lesions by more than or equal to 20% by RECIST criteria 1.0, or 3) decrease in tumor markers by more than or equal to 25% (34).

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, there will be no intra-patient dose escalation, and no patients will be enrolled at the next dose level until three patients enrolled at the previous dose level have completed at least three weeks of therapy. If a DLT is observed in one of the three patients after one cycle, dose escalation will not proceed until six patients in the cohort have been assessed for toxicity after one cycle (34).

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, patients will continue treatment until their disease worsens, their side effects become too severe, or the patient's physician feels it is not in the patient's best interest to continue. A patient may also be discontinued for an intercurrent illness that prevents further administration of treatment. A patient may also choose to discontinue enrollment in the protocol at any time(34). Pre-medication, precautions, route, and schedule for each medication for each medication are described in Table 3.

**TABLE 3: Regimen Description**

| Agent | Premedications; Precautions | Dose | Route | Schedule | Cycle Length |
|---|---|---|---|---|---|
| Bevacizumab | | ** in 100cc of NS | Initial dose is infused over 90 minutes. Infusion may be shortened to 60 minutes if the initial infusion is well tolerated. The third and subsequent infusions may be shortened to 30 minutes if the 60 minute infusion is well tolerated. | Day 1 only | 21 days |
| Temsirolimus | CYP3A4 inhibitors<br>CYP3A4 inducers<br><br>Patients should receive prophylactic intravenous diphenhydramine 25-50mg (or similar antihistamine) approximately 30 minutes before the start of each dose of temsirolimus. | ** in 250cc of NS | The dose is infused over a 30-60 minute period once a week. | Days 1,8, and 15 | 21 days |
| ** Doses as appropriate for assigned dose level. | | | | | |
| *** Testing and drug administration will take place as per protocol unless patient/logistical/medical reasons intervene. | | | | | |

Evaluation During Study

As is standard for investigator initiated protocols in the Department Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, all patients will undergo rigorous evaluation and testing during treatment, including the following:

- Physical examination (including vital signs, weight, performance status) weekly during cycle 1. Thereafter, patients will have a physical examination prior to starting the next cycle.
- Labs to include CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, SGOT[AST], SGPT[ALT], fasting total cholesterol, fasting triglyceride level. These laboratory values will be obtained weekly during cycle 1. Thereafter, patients will have labs drawn prior to starting the the next cycle.
- Urinalysis during week 1 of each cycle.

- Radiologic evaluations and pertinent tumor markers will be repeated after every two cycles of treatment. The same radiologic method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up as reflected in Table 4(34).

**Table 4: Study Calendar**

| Assessment Tool | Baseline | Cycle 1 | | | Cycle 2 | | |
|---|---|---|---|---|---|---|---|
| | | Week | | | Week | | |
| | | 1 | 2 | 3 | 1 | 2 | 3 |
| **Temsirolimus*** | | X | X | X | X | X | X |
| **Bevacizumab**** | | X | | | X | | |
| **History and Physical Exam** | X | X | X | X | X | | |
| **CBC with differential** | X | X | X | X | X | | |
| **Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, Glucose, Calcium, Magnesium** | X | X | X | X | X | | |
| **Albumin, Alkaline Phosphatase, Total Bilirubin, SGOT [AST], SGPT [ALT]** | X | X | X | X | X | | |
| **Urinalysis** | X | X | | | X | | |
| **PT/PTT** | X | | | | | | |
| **Total Cholesterol, Triglyceride** | X | X | X | X | X | | |
| **Serum Pregnancy Test (in women with childbearing potential)** | X | | | | | | |
| **12-lead EKG** | X | | | | | | |
| **Appropriate Radiologic Evaluation** | X | | | | | | X |

* Temsirolimus: Days 1, 8, and 15 every 21 days. See Table 1 for dosing schedule
** Bevacizumab: Day 1 every 21 days. See Table 1 for dosing schedule

Supportive Care: Antiemetics and Growth Factors

Initially, no antiemetics will be used prophylactically. If an individual patient develops nausea and vomiting, therapeutic antiemetics will be used at the discretion of the patient's physician. However, use of antiemetics must be recorded. Prochlorperazine, metocloperamide, promethazine, or equivalent are suggested for grade 1-2 nausea and/or vomiting. 5-$HT_3$

antagonists are suggested for grade 3-4 nausea and/or vomiting. Dexamethasone is not recommended as it is a potent inducer of CYP3A4/5 and may decrease exposure to the active metabolite of temsirolimus, sirolimus. Hematopoietic growth factors may be used following the National Comprehensive Cancer Network (NCCN) guidelines.

Duration of Therapy

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, in the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria are met:

- Progression of disease on combination therapy (bevacizumab and temsirolimus). Exception: If the patient is deriving clinical benefit from the treatment, then the patient may continue on study at the discretion of the principal investigator.
- The development of unacceptable toxicity.
- Physician recommendation for patient removal from study.
- Patient elects to discontinue further treatment on the study medications.
- Intercurrent illness that prevents further administration of treatment.

For those patients achieving complete remission (CR) on combination therapy, they will continue combination therapy until disease progression (34).

Criteria for Removal from the Study

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, patients may be removed from protocol treatment for any of the following reasons:

- Progressive disease (PD) on combination therapy (bevacizumab and

temsirolimus). Patients who develop rapidly PD (as evidenced clinically, radiographically or via tumor markers) prior to the scheduled evaluation every two cycles or six weeks, may be taken off the study at the discretion of the principal investigator. Exception: If the patient is deriving clinical benefit from the treatment, the patient may continue on study at the discretion of the principal investigator.

- The development of unacceptable toxicity.
- Physician recommendation for patient removal from study.
- Patient elects to discontinue further treatment on the study medications.
- Intercurrent illness that prevents further administration of treatment.
- Delay in treatment for > 4 weeks due to treatment-related toxicity or patient non-compliance (34).

## Evaluation of Toxicity and Guidelines for Dose Modification

Our primary objective is to determine the MTDs and DLTs of combination treatment with bevacizumab and temsirolimus in patients with advanced malignancies. Toxicities will be documented at each visit and described according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Safety Considerations

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, DLT is defined as the following:

- Any grade 3 or 4 non-hematologic toxicity (as defined in the NCI CTCAE v3.0), even if expected and believed related to the study medications. Exceptions: nausea and

vomiting responsive to appropriate antiemetic regimens, diarrhea responsive to appropriate antidiarrheal regimens, correctable electrolyte abnormalities, or alopecia.

- Any grade 4 hematologic toxicity lasting 2 weeks or longer (as defined by the NCI-CTCAE v3.0), despite supportive care.
- Any grade 4 nausea or vomiting > 5 days despite maximum anti-nausea regimens.
- Any other grade 3 non-hematologic toxicity including symptoms/signs of vascular leak or cytokine release syndrome
- Any severe or life-threatening complication or abnormality not defined in the NCI-CTCAE that is attributable to the therapy.

The MTD will be defined by DLTs that occur in the first cycle considered the induction phase and lasting three weeks in duration. The use of growth factors is accepted during the clinical study(34).

Dose Modifications

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, if a patient experiences a toxicity at the first dose level, and if the toxicity is known to be related to one drug in the regimen, then a dose reduction of 50% of that drug is permitted after the patient recovers to </= grade 1 toxicity. If, however, a patient experiences a toxicity at the first dose level and it is unclear which drug is the cause of the toxicity, then a dose reduction of 50% of all drugs in the regimen is permitted after the patient recovers to </= grade 1 toxicity(34).

As is standard for investigator initiated protocols in the Department of Investigational

Cancer Therapeutics at M.D. Anderson Cancer Center, at subsequent dose levels, if a patient experiences a toxicity which is known to be related to one drug in the regimen, that drug may be de-escalated to the prior dose level after the patient recovers to </= grade 1 toxicity. If, however, a patient experiences a toxicity for which it is unclear which drug is the cause of the toxicity, both drugs which were dose escalated to the current dose level may be de-escalated to the prior dose levels after the patient recovers to </= grade 1 toxicity(34).

## Criteria for Response and Progression

While the primary objective of this study is to evaluate dose-ranging experience and the toxicity observed, a preliminary descriptive assessment of antitumor efficacy will be made. Evaluation of response will follow the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines 1.0 (35). Response criteria are defined as follows in Tables 5 and 6.

**Table 5: Evaluation of Target Lesions**

| | |
|---|---|
| * Complete Response (CR): | Disappearance of all target lesions |
| * Partial Response (PR): | At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD |
| * Progressive Disease (PD): | At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD (nadir) recorded since the treatment started or the appearance of one or more new lesions |
| * Stable Disease (SD): | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started |

Modified from CTEP website(1). See Appendix 4.

**Table 6: Evaluation of Non-Target Lesions**

| | |
|---|---|
| * Complete Response (CR): | Disappearance of all non-target lesions and normalization of tumor marker level |
| * Incomplete Response/ Stable Disease (SD): | Persistence of one or more non-target lesion(s) or/and 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 (1) |

Modified from CTEP website(1). See Appendix 4.

The best response to therapy is defined as the best response spanning the time from the start of the treatment until disease progression/recurrence. The best response to therapy will be documented as complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD).

**Table 7: Evaluation of Best Overall Response**

| Target lesions | Non-Target lesions | New Lesions | Overall response |
|---|---|---|---|
| **CR** | **CR** | **No** | **CR** |
| **CR** | **Non-CR/Non-PD/not evaluated** | **No** | **PR** |
| **PR** | **Non-CR/Non-PD/not evaluated** | **No** | **PR** |
| **SD** | **Non-CR/Non-PD/not evaluated** | **No** | **SD** |
| **PD** | **Any** | **Yes or No** | **PD** |
| **Any** | **PD** | **Yes or No** | **PD** |
| **Any** | **Any** | **Yes** | **PD** |

Modified from CTEP website (1). See Appendix 4.

## Statistical Considerations

The primary objective of this study is to assess safety and tolerability as well as to define the MTDs of combination treatment with bevacizumab and temsirolimus in patients with advanced cancer. An MTD is defined as the dose level below the dose at which two of six patients experience drug-related DLT in the first cycle. Secondary objectives include a preliminary assessment of antitumor efficacy of each combination (objective response by RECIST criteria) and a preliminary assessment of correlation of surrogate antiangiogenesis markers with antitumor activity.

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, up to an additional 10 patients with biopsiable disease may be entered at the different MTD dose levels after they have been determined for the purpose of exploratory analysis with correlative studies(34). Correlative studies include but are not limited to dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), tumor biopsy, and peripheral blood markers.

As is standard for investigator initiated protocols in the Department of Investigational Cancer Therapeutics at M.D. Anderson Cancer Center, during expansion, at any time > 33% of patients have a DLT, the expansion cohort will be terminated. If the dose expansion is terminated due to >33% of patients having a DLT, then an additional 10 patients may be entered at the next lowest dose level, for the purpose of exploratory analysis with correlative studies. For these additional 10 patients, we will monitor toxicity using the same criteria used in the initial expansion cohorts (34).

# Part III

# Results

## Demographic and Clinical Characteristics

Fifty-six patients enrolled from February 2008 to October 2009. The median age was 57 years, with a range of 19-76 years. At the time of enrollment, most patients had excellent performance status. Eastern Cooperative Oncology Group (ECOG) performance status was 0 for 13 (23%) of the patients, 1 for 36 (64%) of the patients, and 2 for seven (13%) of the patients. The patients had received extensive prior treatment including systemic therapy in 55 patients (98%), surgery in 48 patients (86%), and radiation in 33 patients (59%). The median number of prior systemic therapies was 4, with a range of 0 to 11. Sixteen patients (29%) had previously received treatment on a phase I trial. The most common tumor types enrolled were 10 patients with colorectal cancer (19%), 6 patients with ovarian/peritoneal carcinoma (11%), and 5 patients with melanoma (9%). One patient had primary central nervous system (CNS) tumor at the time of enrollment.

**Table 8 Baseline Demographic & Clinical Characteristics**

| Characteristic | Total (%) |
|---|---|
| Number of patients | 56 |
| Sex | |
| Male | 27 (48%) |
| Female | 29 (52%) |
| ECOG performance status | |
| 0 | 13 (23%) |
| 1 | 36(64%) |
| 2 | 7 (13%) |
| Prior treatment | |
| Surgery | 48 (86%) |
| Radiation | 33 (59%) |
| Chemotherapy | 55 (98%) |
| Phase I trial | 16 (29%) |
| Diagnosis | |
| Colorectal | 10 |
| Ovarian /Peritoneal | 6 |
| Melanoma | 5 |
| Endometrial | 4 |
| Laryngeal | 2 |
| Neuroendocrine | 3 |
| Breast | 4 |
| Parotid Gland | 2 |
| Renal cell | 1 |
| Anal | 1 |
| Cervical - Squamous | 2 |
| Lymphangiomyomatosis | 1 |
| Papillary of the Kidney | 1 |
| Adrenal cortical | 1 |
| Desmoplastic round cell | 1 |
| Prostate | 1 |
| Unknown primary | 1 |
| Ewing's Sarcoma | 1 |
| Granular Cell Sarcoma | 1 |
| Skin - Squamous | 1 |
| Acinic Cell Carcinoma | 1 |
| Nasopharyngeal Carcinoma | 1 |
| Glioblastoma Multiforme | 1 |
| Soft Palate - Squamous | 1 |
| Ampulla of Vater | 1 |
| Oral Tongue - Squamous | 1 |
| Non-small Cell Lung Cancer | 1 |

## Toxicity Assessment

Dose level 13 (bevacizumab 15 mg/kg and temsirolimus 25 mg) was reached and no MTD was obtained as we were able to reach FDA-approved doses of both drugs. Currently, two patients are actively receiving therapy. Thirty-nine patients (70%) experienced no treatment-related toxicity greater than grade 2.

Only one DLT was obtained in dose level 3 (bevacizumab 15 mg/kg and temsirolimus 5mg). The DLT was grade 3 hypertension. Zero of three patients in the expansion cohort at dose level 3 experienced toxicity. Grade 3 or 4 toxicities were observed in 17 patients (30%). Grade 4 toxicities included hypertriglyceridemia (1 patient) and thrombocytopenia (1 patient). Grade 3 toxicities included hypertension (1 patient), hypercholesterolemia (1 patient), hyperglycemia (1 patient), thrombocytopenia (2 patients), mucositis (1 patient), proteinuria (1 patient), leukopenia (1 patient), neutropenia (1 patient) , elevated aspartate aminotransferase (AST) (2 patients), elevated alanine aminotransferase (ALT) (1 patient), fatigue (5 patients), and pneumonitis (1 patient). Table 9 lists the NCI-CTCAE grade 3 and 4 treatment-related toxicities observed for all enrolled patients by dose level.

**Table 9: Treatment-Related Grade 3 and 4 Toxicities***

(* Possibly, Probably, or Definitely treatment-related)

| Dose Level | Number of Patients | Patients with G3/G4 Toxicity | DLTs | Grade 3 and 4 Toxicities |
|---|---|---|---|---|
| 1 | 4 | 0 | 0 | None |
| 2 | 4 | 0 | 0 | None |
| 3 | 7 | 3 | 1 | G3 Hypertension (1); G4 Triglycerides (1); G3 Cholesterol (1) |
| 4 | 4 | 1 | 0 | G3 Hyperglycemia (1) |
| 5 | 4 | 2 | 0 | G3 Mucositis (1); G3 Proteinuria (1) |
| 6 | 4 | 2 | 0 | G3 Leukopenia (1); G3 Neutropenia (1); G3 AST (1) |
| 7 | 4 | 0 | 0 | None |
| 8 | 5 | 2 | 0 | G4 Thrombocytopenia (1); G3 Fatigue (1) |
| 9 | 4 | 2 | 0 | G3 Fatigue (1); G3 Thrombocytopenia (1) |
| 10 | 3 | 2 | 0 | G3 Fatigue (1); G3 ALT (1); G3 AST (1) |
| 11 | 3 | 0 | 0 | None |
| 12 | 4 | 1 | 0 | G3 Fatigue (1); |
| 13 | 6 | 2 | 0 | G3 Fatigue (1); G3 Thrombocytopenia (1); G3 Pneumonitis (1) |

Three patients died while enrolled on the study. The cause of death in each case was determined to be unrelated to the study medications. The details of the cases are described below:

1) Patient # 27, a 53-year old man with squamous cell carcinoma of the larynx with locally advanced disease involving the soft tissues of the neck and cervical lymph nodes was enrolled on dose level 6 (bevacizumab 15 mg/kg and temsirolimus 12.5 mg). The patient

was treated in the hospital and on day 12 of the first cycle had a carotid artery blow-out that was fatal.

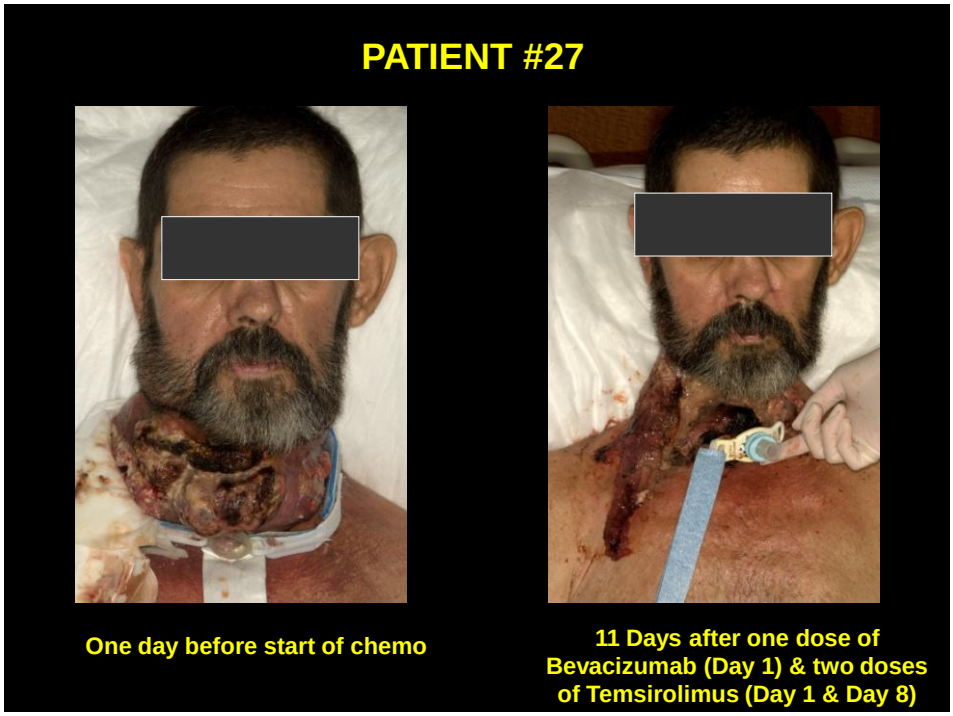


**Figure 4a: Images for Patient #27**

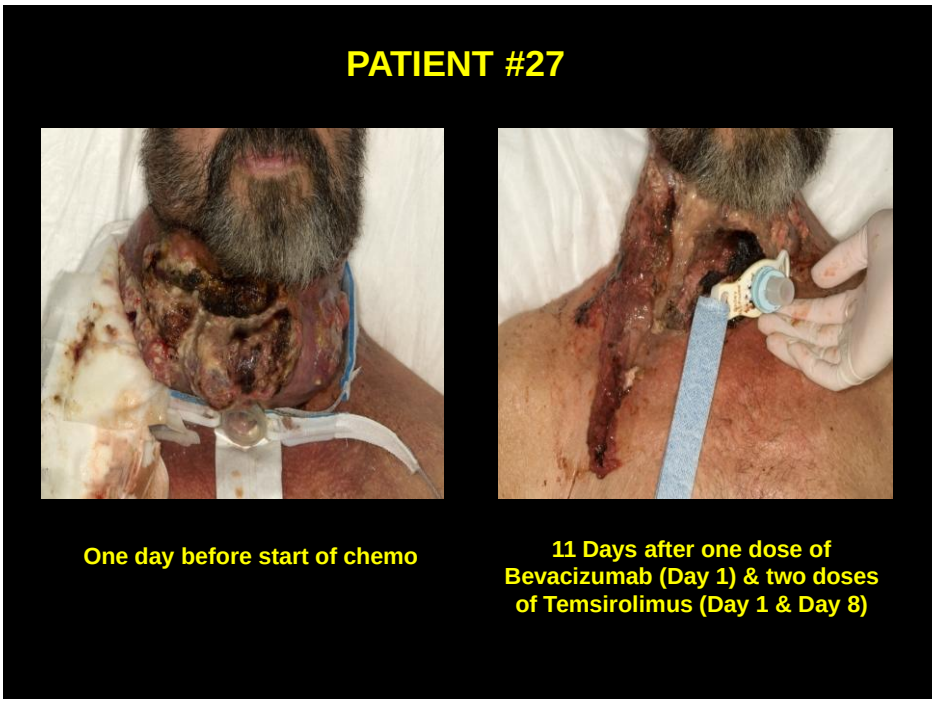


**Figure 4b: Images for Patient #27**

2) Patient #15, a 51-year old woman with rectal cancer metastatic to the lungs, bones and spleen was enrolled on dose level 3 (bevacizumab 15 mg/kg and temsirolimus 5 mg). The patient was admitted to the hospital on day 15 of the first cycle for failure to thrive, severe fatigue, nausea and abdominal pain. She had only received cycle 1, day 1 therapy with bevacizumab and temsirolimus. She did not receive cycle 1, day 8 temsirolimus secondary to severe fatigue. During the hospital work-up, she was found to have a rectal stricture and stent was placed by gastroenterology on cycle 1, day 18. The patient subsequently developed pseudo-obstruction and had a decompression tube placed by gastroenterology on cycle 1, day 29. On cycle 1, day 31, she became hypotensive with blood pressures refractory to pressors and aggressive intravenous fluids. She also had decreased hemoglobin on labs though no source of bleeding was identified. The family opted for supportive measures only. She died later the next day on cycle 1, day 32.
3) Patient #32, a 55-year old woman with endometrial cancer metastatic to the peritoneum was enrolled on dose level 8 (bevacizumab 7.5 mg/kg and temsirolimus 25 mg). On cycle 12, day 13 she was admitted to an outside hospital for severe abdominal pain. She was found to have sepsis and peritonitis and died later that day on cycle 12, day 13 with supportive measures in place.

## Antitumor Activity

Forty-two of the 56 patients were measurable by RECIST (Figure 5). Ten patients were assigned a value of 21% for clinical progression or new lesions. Among the remaining four patients, three patients were assigned a value of 1% as they were evaluable but not measurable

per RECIST but had stable disease (+), and one patient (patient #27 shown in Figures 4a and 4b) had a remarkable clinical response but died before restaging evaluation was performed.

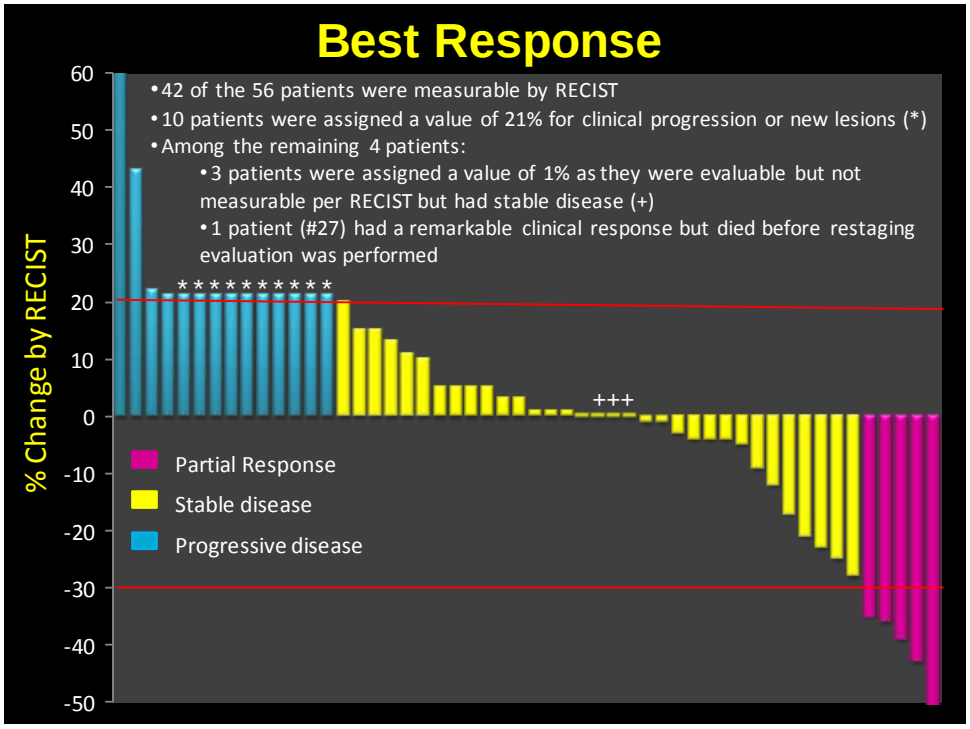


**Figure 5: Best Response by RECIST**

Five patients achieved a partial response (PR). The details of each case are described below:

1) Patient #21, a 60-year old woman with endometrial cancer metastatic to liver, pelvis, and pelvic lymph nodes, was enrolled on dose level 5 (bevacizumab 7.5 mg/kg and temsirolimus 12.5 mg). The patient's previous treatments include: surgery, carboplatin, Taxol, Doxil, EZN-2208 (pegylated irinotecan) and palliative radiation. The patient had a PR of 39% and received treatment for 12 cycles (9 months). Figure 5 illustrates the radiographic images of the patient.

2) Patient #24, a 33-year old woman with squamous cell carcinoma of the cervix, metastatic to the mediastinum and retroperitoneal lymph nodes, enrolled on dose level 6 (bevacizumab 15 mg/kg and temsirolimus 12.5 mg). The patient's previous treatments include: cisplatin, Taxol, radiation, brachytherapy, topotecan, Xeloda, and Tarceva. The patient had a PR of 43% and received treatment for 6 cycles (4.5 months). Figures 7 and 8 illustrate the radiographic images of the patient.
3) Patient #29, a 51-year old woman with lymphangioleimyomatosis with lymph node involvement of the left supraclavicular, right retrocrural, aorto-pulmonary window, bilateral common iliac region, and left paraaortic and aortocaval space. The patient was enrolled on dose level 7 (bevacizumab 2.5 mg/kg and temsirolimus 20 mg). The patient had had multiple surgeries. The patient had a PR of 68% and received 8 cycles (6 months) of therapy on protocol. The patient is still receiving treatment at home off-protocol as the burden and expensive of travel became too much. Figure 9 illustrates the radiographic images of the patient.
4) Patient #44, a 70-year old woman with acinic cell carcinoma of the right cheek metastatic to the lungs and bone, enrolled on dose level 11 (bevacizumab 5 mg/kg and temsirolimus 25 mg). The patient's previous treatments include: surgery, radiation, farnesyltransferase inhibitor (protocol ID98-369), carboplatin, Taxol, Benzimate Fungicide, FTS protocol (direct RAS inhibitor), patupilone, and AZD8330 (MEK inhibitor). The patient had a PR of 30% and received treatment for 10 cycles (7.5 months). Figure 10 illustrates the radiographic images of the patient.
5) Patient #57, a 49-year old man with squamous cell carcinoma of the oral tongue metastatic to lymph nodes in the right neck, right supraclavicular fossa, mediastinum and

right axilla, enrolled on dose level 12 (bevacizumab 10 mg/kg and temsirolimus 25 mg). The patient's previous treatments include: surgery, radiation, Herceptin, Taxol, cisplatin, carboplatin, sorafenib, IMC-A12 (insulin growth factor receptor [IGFR] inhibitor), and OSI-906 (IGFR inhbititor). The patient had a PR of 35% and received treatment for 5 cycles (3.75 months). Figure 11 illustrates the radiographic images of the patient.

**Table 10: Partial Responses**

| Pt # | Tumor Type | Dose Level | Best Response | Cycles Received |
|---|---|---|---|---|
| 21 | Endometrial | 5 | -39% | 12 |
| 24 | Cervical - Squamous | 6 | -43% | 6 |
| 29 | Lymphangioleiomyomatosis | 7 | -68% | 8+ |
| 44 | Acinic Cell | 11 | -36% | 10 |
| 57 | Oral Tongue - Squamous | 12 | -35% | 5 |

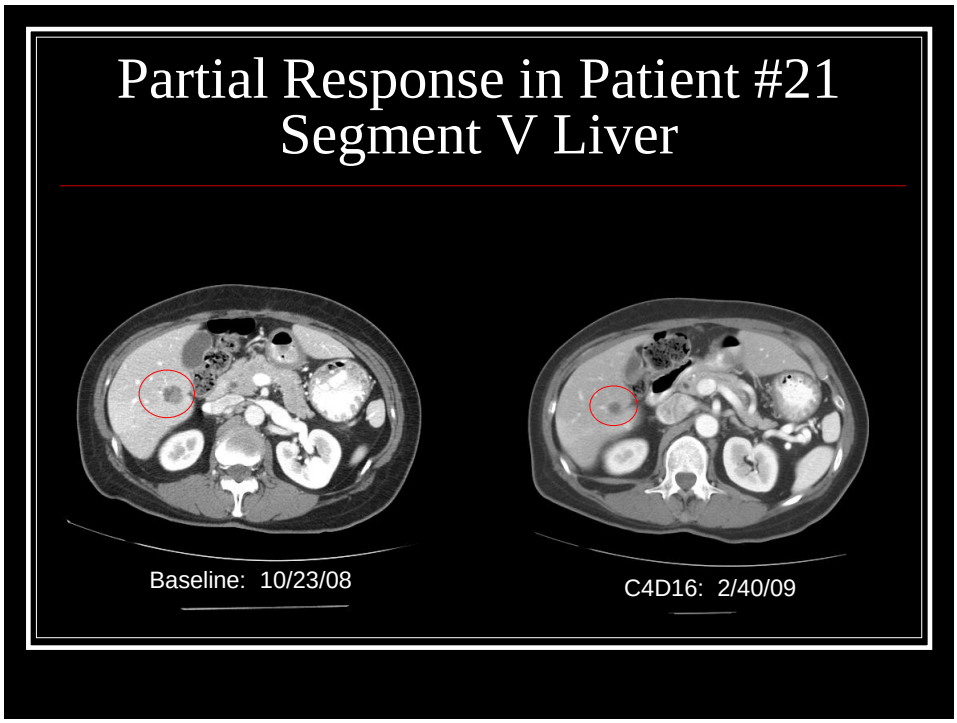


**Figure 6: Partial Response in Patient #21, Segment V Liver**

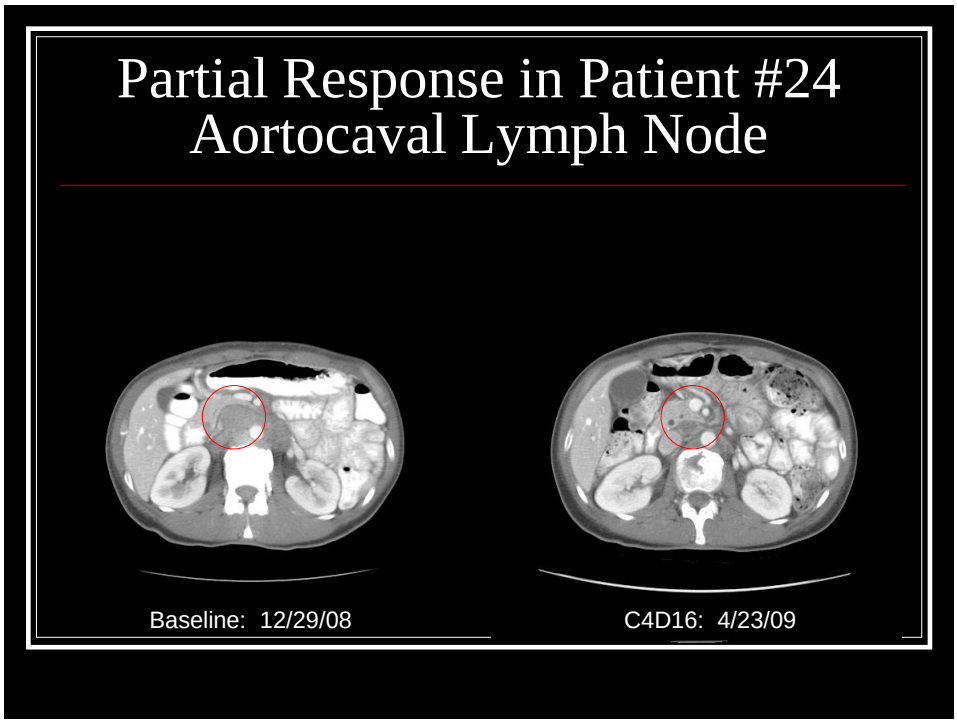


**Figure 7: Partial Response in Patient #24, Aortocaval Lymph Node**

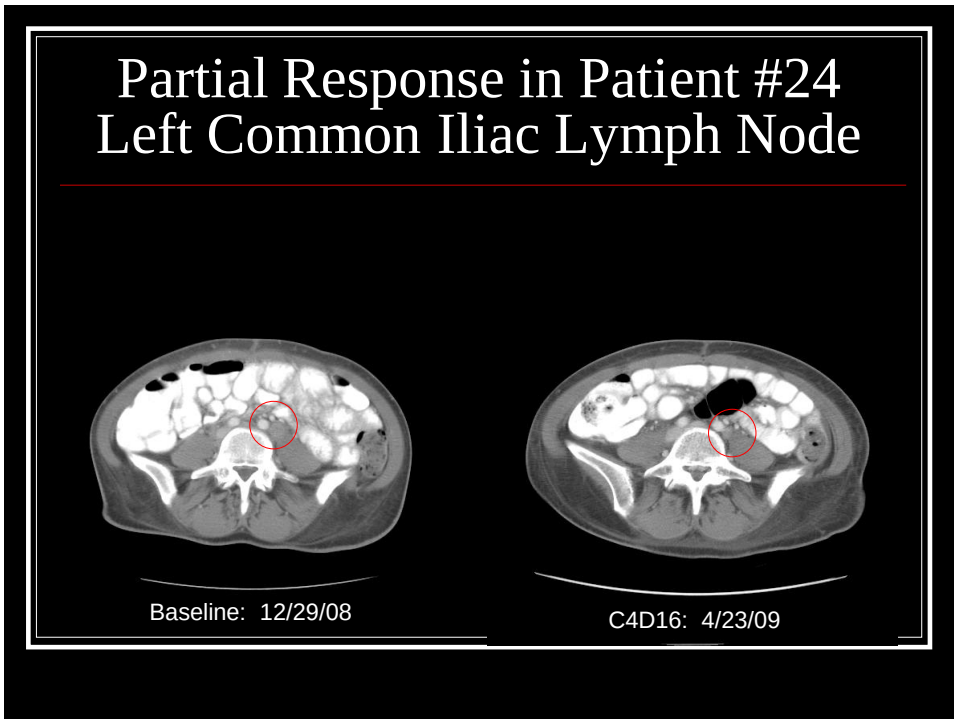


**Figure 8: Partial Response in Patient #24, Left Common Iliac Lymph Node**

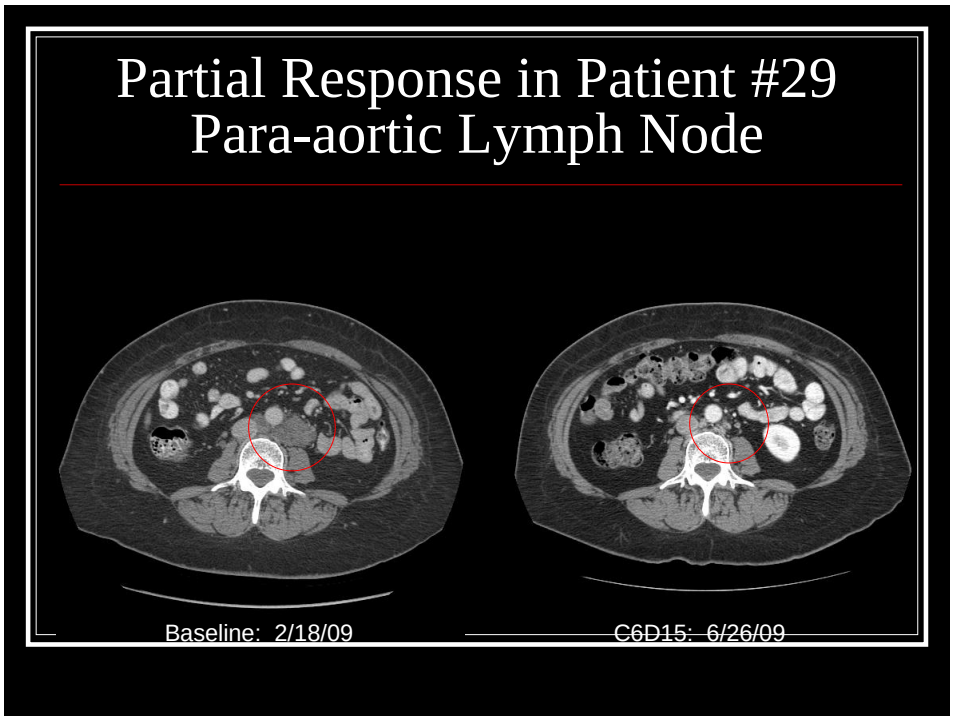


**Figure 9: Partial Response in Patient #29, Para-aortic Lymph Node**

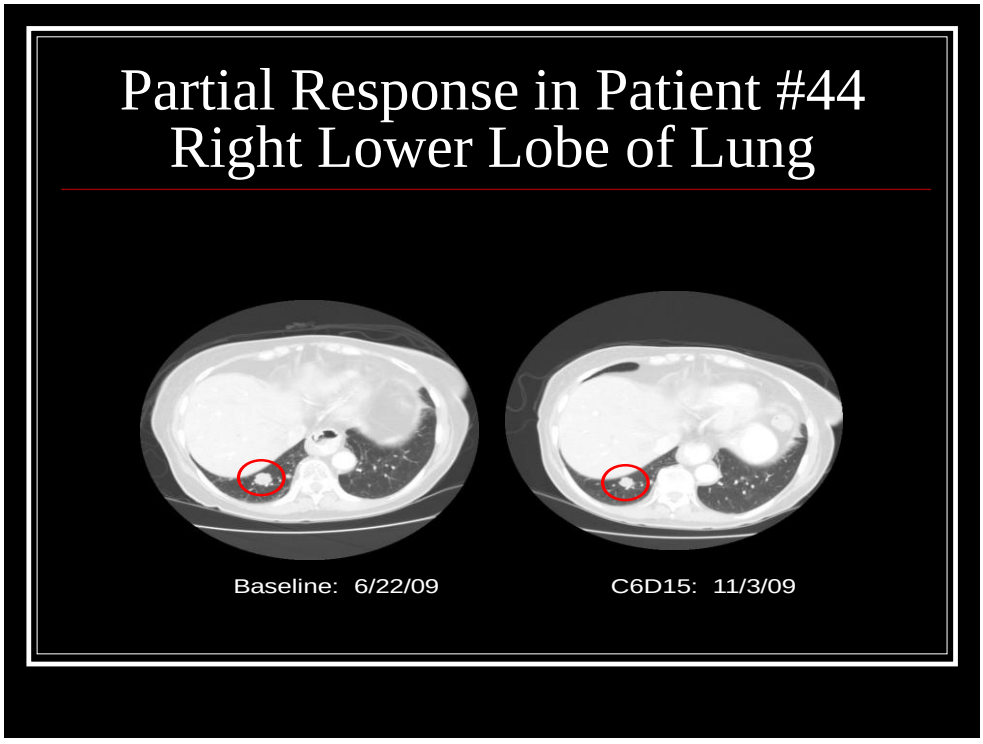


**Figure 10: Partial Response in Patient #44, Right Lower Lobe of Lung**

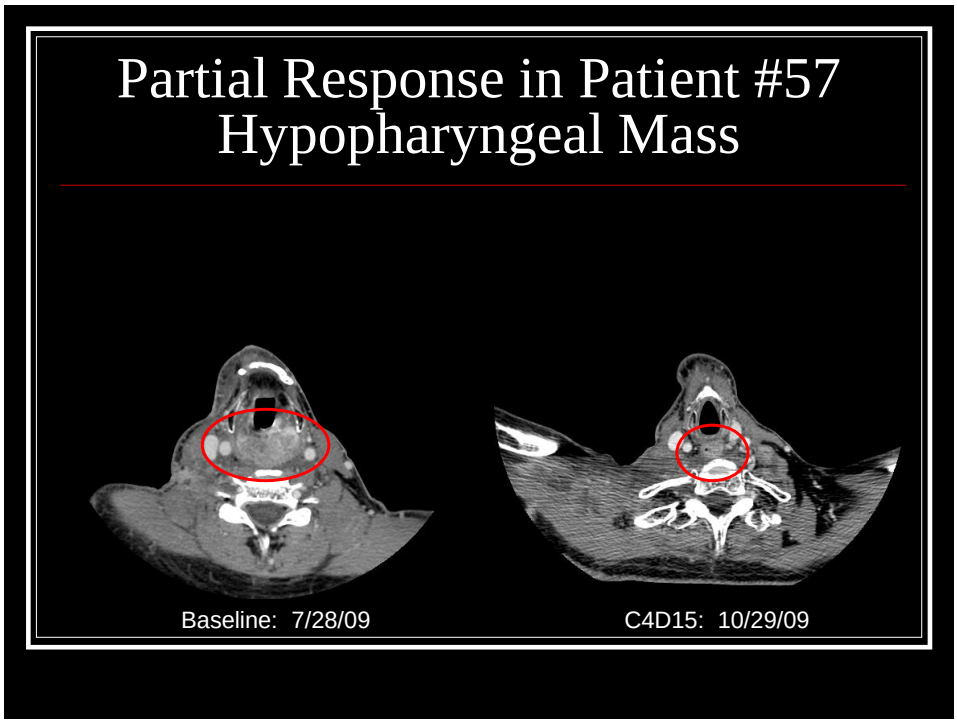


**Figure 11: Partial Response in Patient #57, Hypopharyngeal Mass**

Stable disease lasting longer than six months was observed in 7 patients (13%) listed in table 11 with details regarding the dose level, number of cycles received, and best response by RECIST. Of all enrolled patients, the median cycles received was 4, the range was 1 to 14 cycles. Thirty-five patients (63%) received more than 2 cycles.

**Table 11: Stable Disease Lasting ≥ 6 Months**

| Pt # | Tumor Type | Dose Level | Best Response | Cycles Received | Comments |
|---|---|---|---|---|---|
| 6 | Primary Peritoneal Carinoma | 2 | 0% | 8 | |
| 13 | Ovarian | 3 | -7% | 12 | |
| 17 | Colorectal | 4 | -4% | 14 | |
| 22 | Parotid Cancer | 5 | Not measurable | 12 | Progressive disease in the lung |
| 31 | Colorectal | 7 | -4% | 8 | |
| 32 | Endometrial | 8 | Not measurable | 12 | Died from non-neutropenic sepsis. |
| 34 | Parotid Cancer | 8 | 0% | 11 | Pt taken off study for clinical progression as evidenced by oropharyngeal bleeding from tumor. |

# Part V

# Conclusions, Discussion, and Future Directions

This phase I study of combined bevacizumab and temsirolimus successfully completed dose escalation to the highest specified dose level, dose level 13, which consisted of FDA-approved doses of both drugs (bevacizumab 15 mg/kg and temsirolimus 25 mg). Escalation beyond the FDA-approved doses was not included in this trial design because insurance companies would not be expected to reimburse the cost of the drugs above the FDA-approved doses. No DLTs were observed at the highest dose level. The recommended phase II dose for the combination is bevacizumab 15 mg/kg and temsirolimus 25 mg.

The study design was efficient and allowed for exploration of multiple dose levels. My hypothesis that our new trial design would facilitate identification of more than one MTD was not achieved likely because the maximum dose of each targeted drug proved to be tolerable in combination due to non-overlapping toxicities. Going forward, I have plans to apply this trial design in other investigator initiated protocols combining targeted agents.

Combination therapy with bevacizumab and temsirolimus showed safety and excellent tolerance. Thirty-nine patients (70%) experienced no treatment-related toxicity greater than grade 2 and only one DLT was obtained throughout the trial. A minority of patients, 17 patients (30%), experienced grade 3 or 4 toxicities, most of which were cytopenias, dyslipidemia, elevated liver function tests (ALT/AST) or fatigue, and attributed to temsirolimus.

Partial responses were seen in five of 56 patients (9%) and stable disease lasting more than 6 months was seen in 7 patients (13%). This is especially significant when taking into consideration the extensive number of prior therapies of the patients involved in this study, including systemic therapy in 55 patients (98%) with the median number of prior systemic therapies at four, with a range of zero to 11. Furthermore, 16 patients (29%) had previously received treatment on a phase I trial.

Two of five (40%) of the patients with PRs were found to have either a phosphatidylinositol 3-kinase (PI3 kinase) mutation or loss of phosphatase and tensin homolog (PTEN). None of the patients with stable disease lasting > 6 months were found to have PI3 kinase mutations and PTEN loss analysis was not performed on any of these patients. Please note that PTEN loss was recently added in September of 2009 as a Clinical Laboratory Improvement Amendments (CLIA)-certified, immunohistochemistry (ICH) test by the Pathology Department at M. D. Anderson Cancer Center.

Mutations in PI3 kinase result in activation of the PI3 kinase/AKT/mTOR pathway (Figure 12) and are present in a variety of tumor types(36, 37). Janku et al. recently published a response rate of 35% in heavily pretreated patients with somatic PI3 kinase mutations when treated with PI3kinase/AKT/mTOR pathway inhibitors(38). Temsirolimus, as previously mentioned, is an mTOR inhibitor. If we were to further evaluate mutational status and response the following is seen:

- PI3 kinase mutation present/Total number of PI3 kinase mutations tested = 1/27 = 4%.
- PTEN loss mutation present/Total number of PTEN loss mutations tested = 1/2 = 50%.
- (CR/PR)/Total Patients = 5/56 = 9%.
- (CR/PR + SD > 6 months)/Total patients = 12/56 = 21%.
- (Total with CR/PR + SD > 6 months) AND (PI3 kinase mutation present OR PTEN loss)/(Total with CR/PR + SD > 6 months) = 2/12 = 17%.
- (Total with CR/PR + SD > 6 months) AND (PI3 kinase mutation present OR PTEN loss)/(Total with PI3 kinase mutation OR PTEN loss) = 2/2=100%

To summarize, 40% of patients with CR/PR and 17% of patients with SD > 6 months and CR/PR had PI3 kinase mutation or PTEN loss. Of those tested for PI3 kinase mutation or PTEN loss and who showed positivity for either test, 100% had CR/PR or SD > 6 months.

The protocol was written to allow us to expand enrollment by a total of 14 patients with a tumor type where response, as defined by one or more of the following: 1) stable disease for more than or equal to four months, 2) decrease in the sum of target lesions by more than or equal to 20% by RECIST criteria, or 3) decrease in tumor markers by more than or equal to 25%, is seen. Based on the results of this trial summarized in Table 14, we have expanded enrollment to patients with squamous cell of the head and neck, parotid cancer, endometrial cancer, cervical cancer, colorectal cancer, ovarian/primary peritoneal/fallopian tube cancer, acinic cell carcinoma/salivary gland cancer and lymphangioleiomyomatosis.

In conclusion, the combination of bevacizumab and temsirolimus is well tolerated and has demonstrated clinical activity in patients with advanced malignancy having undergone extensive prior therapy. Because partial responses and prolonged stable disease (SD > 6 months) have been seen in a variety of tumor types (as above), further evaluation in these tumor types at the recommended phase II dose is warranted. Additionally, it will be interesting to evaluate the incidence of PI3 kinase mutations or PTEN loss and correlate this with response to this therapy.

## Table 12: Partial Responses and Mutation Status

| Pt # | Tumor Type | Dose Level | Best Response | Cycles Received | PTEN Loss | PI3 Kinase Mutation | RAS Mutation | RAF Mutation |
|---|---|---|---|---|---|---|---|---|
| 21 | Endometrial | 5 | -39% | 12 | ND | Y | ND | ND |
| 24 | Cervical - Squamous | 6 | -43% | 6 | ND | N | ND | ND |
| 29 | Lymphangioleiomyomatosis | 7 | -68% | 8+ | ND | N | ND | ND |
| 44 | Acinic Cell | 11 | -36% | 10 | ND | N | ND | ND |
| 57 | Oral Tongue - Squamous | 12 | -35% | 5 | Y | N | ND | N |

**ND = not done; N = No; Y= Yes**

## Table 13: Stable Disease Lasting ≥ 6 Months and Mutation Status

| Pt # | Tumor Type | Dose Level | Best Response | Cycles Received | PTEN Loss | PI3 Kinase Mutation | RAS Mutation | RAF Mutation |
|---|---|---|---|---|---|---|---|---|
| 6 | Primary Peritoneal Carinoma | 2 | 0% | 8 | ND | N | ND | ND |
| 13 | Ovarian | 3 | -7% | 12 | ND | N | ND | ND |
| 17 | Colorectal | 4 | -4% | 14 | ND | N | ND | ND |
| 22 | Parotid Cancer | 5 | Not Measurable | 12 | ND | N | ND | ND |
| 31 | Colorectal | 7 | -4% | 8 | ND | N | Y | ND |
| 32 | Endometrial | 8 | Not Measurable | 12 | ND | N | N | ND |
| 34 | Parotid Cancer | 8 | 0% | 11 | ND | N | ND | ND |

**ND = not done; N = No; Y= Yes**

## Table 14: Stable Disease Lasting ≥ 6 Months or Partial Remissions by Tumor Type

| Tumor Type | SD≥ 6 months or PR (N) | Total Treated (N) | Percent Response (%) |
|---|---|---|---|
| Endometrial | 2 | 4 | 50 |
| Cervical - Squamous | 1 | 2 | 50 |
| Lymphangioleiomyomatosis | 1 | 1 | 100 |
| Acinic Cell | 1 | 1 | 100 |
| Oral Tongue - Squamous | 1 | 1 | 100 |
| Ovarian | 2 | 6 | 33 |
| Colorectal | 2 | 10 | 20 |
| Parotid Cancer | 2 | 2 | 100 |

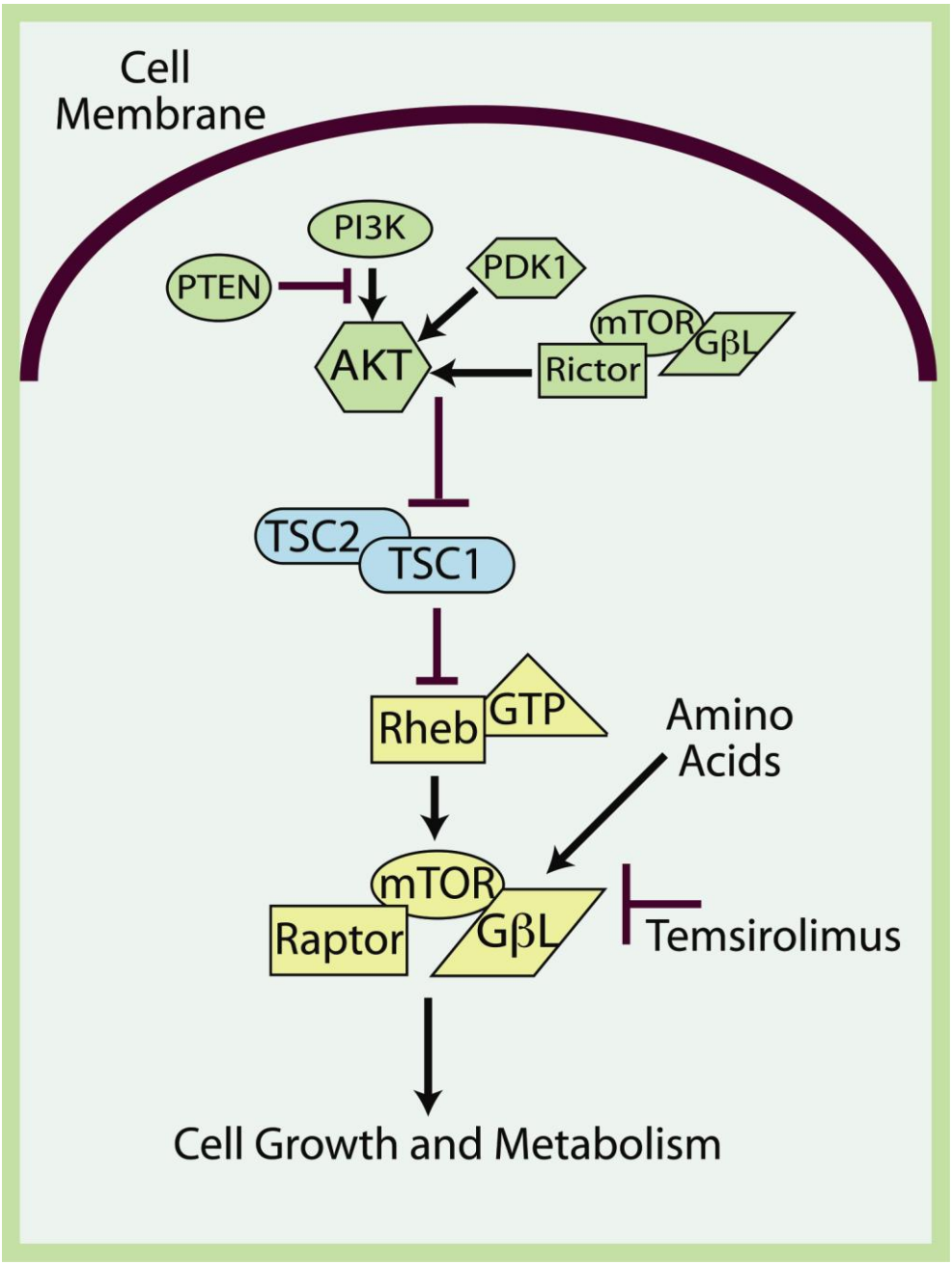


**Figure 12: PI3 kinase/AKT/mTOR pathway**

# Part VI

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# Part VII

# Appendices

# Appendix 1: Scales for Performance Status Evaluation

| ECOG Performance Status (94) | |
|---|---|
| **Grade** | **ECOG** |
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 5 | Dead |

| Karnofsky Performance Status Scale Definitions Rating (%) Criteria (95) | | |
|---|---|---|
| Able to carry on normal activity and to work; no special care needed. | 100 | Normal no complaints; no evidence of disease. |
| | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| | 80 | Normal activity with effort; some signs or symptoms of disease. |
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. | 70 | Cares for self; unable to carry on normal activity or to do active work. |
| | 60 | Requires occasional assistance, but is able to care for most of his personal needs. |
| | 50 | Requires considerable assistance and frequent medical care. |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | 40 | Disabled; requires special care and assistance. |
| | 30 | Severely disabled; hospital admission is indicated although death not imminent. |
| | 20 | Very sick; hospital admission necessary; active supportive treatment necessary. |
| | 10 | Moribund; fatal processes progressing rapidly. |
| | 0 | Dead |

# Appendix 2: Permission to Use HIF-1α Pathway Figure

**From:** Gillette,Lysaann N
**Sent:** Thursday, July 22, 2010 8:43 AM
**To:** 'daniel.peet@adelaide.edu.au'
**Cc:** Piha-Paul,Sarina Anne
**Subject:** RE: Request for permission to use HIF1 figure

Dr. Peet,

I do thank you for the quick reply. My physician's name is Dr. Sarina Piha-Paul , the nature is that she is defending her thesis to get her Masters degree, and the title of the thesis is **An Innovative Phase I Trial Design Allowing for the Identification of Multiple Potential Maximum Tolerated Doses with Combination Therapy of Targeted Agents**. Again, I thank you for allowing us to use your HIF1 figure.

Lysaann Gillette
Administrative Assistant to:
Siqing Fu, MD, PhD
Sarina Piha-Paul, MD
UT M.D. Anderson Cancer Center
Division of Cancer Medicine
Department of Investigational Cancer Therapeutics
1515 Holcombe Boulevard, Unit 455
Houston, Texas 77030
Phone (713) 745-0147
Fax (713) 745-3855

**From:** Daniel Peet [mailto:daniel.peet@adelaide.edu.au]
**Sent:** Wednesday, July 21, 2010 5:55 PM
**To:** Gillette,Lysaann N
**Subject:** RE: Request for permission to use HIF1 figure

Dear Lysaann,

Yes, I am happy for the physician to use this figure in their thesis. Could you please first inform me of the name of the physician and also the nature and title of the thesis? Please just acknowledge that the figure is used with my permission (my details below, although they don't all need to be included).

Best Regards,

Dan

---

Dan Peet, PhD
Senior Lecturer
School of Molecular and Biomedical Science,
University of Adelaide
Adelaide, SA, 5005
AUSTRALIA

Email: daniel.peet@adelaide.edu.au
Ph: +61 8 8303 5367
Fax: +61 8 8303 4362

**From:** Gillette,Lysaann N [mailto:lgillette@mdanderson.org]
**Sent:** Thursday, 22 July 2010 7:16 AM
**To:** 'daniel.peet@adelaide.edu.au'
**Cc:** Piha-Paul,Sarina Anne
**Subject:** Request for permission to use HIF1 figure

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Lysaann Gillette
Administrative Assistant to:
Siqing Fu, MD, PhD
Sarina Piha-Paul, MD
UT M.D. Anderson Cancer Center
Division of Cancer Medicine
Department of Investigational Cancer Therapeutics
1515 Holcombe Boulevard, Unit 455
Houston, Texas 77030
Phone (713) 745-0147
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# Appendix 3: Permission to Use Illustration of Combination Doses Figure

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**Sent:** Thursday, July 29, 2010 10:32 AM
**To:** Berry,Donald; Huang,Xuelin
**Cc:** Piha-Paul,Sarina Anne
**Subject:** RE: Request for permission to use An Illustration of Combination Doses

Dr. Berry and Dr. Huang,

On behalf of Dr. Piha-Paul, I would like to thank you for granting her permission to use your illustration.

Lysaann Gillette
Administrative Assistant to:
Siqing Fu, MD, PhD
Sarina Piha-Paul, MD
UT M.D. Anderson Cancer Center
Division of Cancer Medicine
Department of Investigational Cancer Therapeutics
1515 Holcombe Boulevard, Unit 455
Houston, Texas 77030
Phone (713) 745-0147
Fax (713) 745-3855

**From:** Berry,Donald
**Sent:** Wednesday, July 28, 2010 8:20 PM
**To:** Gillette,Lysaann N
**Cc:** Huang,Xuelin; Piha-Paul,Sarina Anne
**Subject:** Re: Request for permission to use An Illustration of Combination Doses

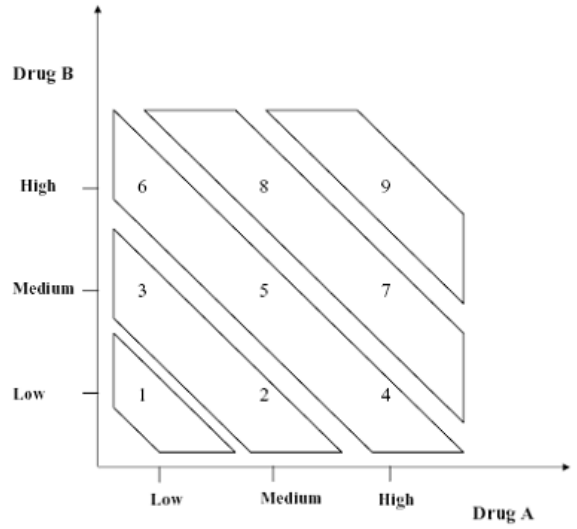
She has our permission. Don Berry

**From:** Gillette,Lysaann N
**Sent:** Wednesday, July 28, 2010 4:37 PM
**To:** Berry,Donald; Huang,Xuelin
**Cc:** Piha-Paul,Sarina Anne
**Subject:** Request for permission to use An Illustration of Combination Doses

Dr. Donald Berry and Dr. Xuelin Huang,

I'm writing in hopes that you will be able to assist me at your earliest convenience before July 30, 2010. Dr. Piha-Paul would like to have permission to use your Illustration of Combination Doses (as shown below) in her thesis and would like to know how to properly credit and reference you. Would you kindly assist? I do thank you.

**An Illustration of Combination Doses**




Lysaann Gillette
Administrative Assistant to:
Siqing Fu, MD, PhD
Sarina Piha-Paul, MD
UT M.D. Anderson Cancer Center
Division of Cancer Medicine
Department of Investigational Cancer Therapeutics
1515 Holcombe Boulevard, Unit 455
Houston, Texas 77030
Phone (713) 745-0147
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# Appendix 4: Phase I Combination 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:

   a) Protocol Submission Worksheet: available at http://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).

**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 Study of *CTEP IND Agent* in Combination with *Other Agent*(s) in *Solid Tumors/Study Disease*

*Use Simplified Disease Classification (SDC) terminology for study disease. Please refer to the CTEP Web site (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).*

***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. 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:**
*(if applicable)*
*Name*
*Address*
*Address*
*Telephone*
*Fax*
*e-mail address*

**Study Coordinator:**
*(if applicable)*
*Name*
*Address*
*Address*
*Telephone*
*Fax*
*e-mail address*

**Responsible Research Nurse:**
*Name*
*Address*
*Address*
*Telephone*
*Fax*
*e-mail address*

**Responsible Data Manager:**
*Name*
*Address*
*Address*
*Telephone*
*Fax*
*e-mail address*

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

*Please list agent name, NSC #, IND #, and supplier(s) of any other investigational agent(s).*

*Please list all commercially available agents and their suppliers.*

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

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

## SCHEMA

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

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

## TABLE OF CONTENTS

## 1. OBJECTIVES

### 1.1. Primary Objectives

*Please insert primary protocol objectives.*

### 1.2. Secondary Objectives

*Please insert secondary protocol objectives, if pertinent.*

## 2. BACKGROUND

### 2.1 CTEP-Supplied Investigational Agent(s)

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

#### 2.1.1 ***CTEP IND Agent #1***

#### 2.1.2 ***CTEP IND Agent #2***

### 2.2 ***Other Agent(s)***

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

### 2.3 ***Study Disease***

*For disease-specific studies, please provide background information on the study disease.*

### 2.4 Rationale

*Please provide the background and rationale for this combination therapy (in this disease).*

### 2.5 Correlative Studies Background

*Please provide background information on <u>each</u> planned correlative study including the biologic rationale and hypothesis as well as the relevant preclinical and clinical (if available) data. Refer to "Guidelines for Correlative Studies in Clinical Trials" (http://ctep.cancer.gov/protocolDevelopment/templates_applications.htm). If this trial includes no correlative studies, this section should be marked "N/A".*

## 3. PATIENT SELECTION

### 3.1 Eligibility Criteria

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

*OR*

Patients must have histologically or cytologically confirmed *<u>Study Disease</u>*. *Please specify eligible disease(s)/stage(s) using the CTEP Simplified Disease Classification (<u>http://ctep.cancer.gov/protocolDevelopment/codes_values.htm</u>).*

3.1.2 *Please state allowable type and amount of prior therapy. Define as appropriate any limitations on prior therapy and the time from last prior regimen (e.g., no more than 6 cycles of an alkylating agent; no more than 450 mg/m$^2$ doxorubicin for agents with expected cumulative cardiotoxicity). Include separate definitions for duration as needed (e.g., at least 4 weeks since prior chemotherapy or radiation therapy, 6 weeks if the last regimen included BCNU or mitomycin C). Include site/total dose for prior radiation exposure as needed (e.g., no more than 3000 cGy to fields including substantial marrow).*

3.1.3 Age <u>≥</u>18 years. *Please state reason for age restriction. If applicable, the following text can be used.*

Because no dosing or adverse event data are currently available on the use of *<u>CTEP IND Agent</u>* in combination with *<u>[other agents]</u>* in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric phase 1 combination trials.

3.1.4 ECOG performance status <u>≤</u>2 (Karnofsky <u>≥</u>60%, see Appendix A).

3.1.5 Life expectancy of greater than *<u>[#weeks or months]</u>*.

3.1.6 Patients must have normal organ and marrow function as defined below:

- leukocytes <u>≥</u>3,000/mcL
- absolute neutrophil count <u>≥</u>1,500/mcL

- platelets ≥100,000/mcL
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance ≥60 mL/min/1.73 $m^2$ for patients with creatinine levels above institutional normal.

3.1.7 *Please insert other appropriate eligibility criteria.*

3.1.8 *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 as well as other therapeutic agents used in this trial 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.

3.1.9 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.

3.2.2 Patients may not be 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(s)* or other agents used in study.

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). 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*. These potential risks may also apply to other agents used in this study.

*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). 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.

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.

## 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.*

### 4.1 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 *[Name of Form(s)]* can be found in Appendix *(Appendix #)*.

Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. 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) except for Group studies.

### 4.2 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 Study Coordinator:

- Copy of required laboratory tests
- Signed patient consent form
- HIPAA authorization form
- *Other appropriate forms (e.g., Eligibility Screening Worksheet, Registration Form)*

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

- assign a patient study number
- assign the patient a dose
- register the patient on the study
- 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 Agent Administration

Treatment will be administered on an _*inpatient/outpatient*_ basis. Reported adverse events and potential risks for _*CTEP IND Agent(s)*_ and _*Other Agent(s)*_ are described in Section 7. Appropriate dose modifications for _*CTEP IND Agent(s)*_ and _*Other Agent(s)*_ are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

*State the starting dose of each agent and describe the dose escalation scheme and treatment regimen.* ***Use exact doses rather than percentages****. If appropriate, a table may be used to describe the regimen; see an example below. Please refer to the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/policies_nomenclature.htm) for Guidelines for Treatment Regimen Nomenclature and Expression.*

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

*Example:*

| ***REGIMEN DESCRIPTION*** | | | | | |
|---|---|---|---|---|---|
| ***Agent*** | ***Premedications; Precautions*** | ***Dose*** | ***Route*** | ***Schedule*** | ***Cycle Length*** |
| *Agent X* | *Premedicate with dexamethasone for 3 days prior to _Agent X_.* | *** in 500 cc NS* | *IV over 2 hours* ***before*** *Agent Y* | *Days 1-3, week 1* | *28 days (4 weeks)* |

| | | | | | |
|---|---|---|---|---|---|
| **4.** *Agent Y* | *Avoid exposure to cold (food, liquids, air) for 24 hr after each dose.* | *** in 250 cc D5W* | *IV 1 hr after completion of Agent A through separate IV line* | *Days 1-3, week 1* | |
| *Agent Z* | *Take with food.* | *** tablet* | *PO in the a.m.* | *Daily, weeks 1 and 2* | |
| *** Doses as appropriate for assigned dose level.* | | | | | |

5.1.1 *CTEP IND Agent(s)*

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

5.1.2 *Other Agent(s)*

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

5.1.3 *Other Modality(ies) or Procedures*

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

## 5.2 Definition of Dose-Limiting Toxicity

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

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above. *An accelerated titration design of the investigator's choice may be substituted. An example can be found on the following Web site (http://linus.nci.nih.gov/~brb/Methodologic.htm).*

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

## 5.3 General Concomitant Medication and Supportive Care Guidelines

*Please state guidelines for use of concomitant medications or any additional appropriate supportive care medications or treatments. The potential for interaction with the cytochrome P450 system should be addressed if applicable. Please use or modify the following paragraph as appropriate.*

Because there is a potential for interaction of *_CTEP IND Agent(s)_* with other concomitantly administered drugs through the cytochrome P450 system, the case report form 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 selected CYP450 isoenzymes.

## 5.4 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.

### 5.5 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.

### 5.6 Criteria for Removal from Study

*Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.*

## 6. DOSING DELAYS/DOSE MODIFICATIONS

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

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

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

***Note:*** *All treatment modifications must be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose.*
*Dose modifications/treatment delays for _CTEP IND Agent(s)_ and _Other Agent(s)_ may be presented separately or together, as appropriate. Use of a table format is recommended if applicable.*

## 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 (via AdEERS) **in addition** to routine reporting.

## 7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

*Sections provided below should be used or deleted as necessary.*

### 7.1.1 CAEPRs for CTEP-Supplied Investigational Agent(s)

*The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete 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, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and **italicized** text. This subset of AEs (the ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm) for further clarification. The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.*

#### 7.1.1.1 CAEPR for _(*CTEP IND Agent #1*)_

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

#### 7.1.1.2 CAEPR for _(*CTEP IND Agent #2*)_

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

### 7.1.2 Adverse Event List(s) for _[*Other Investigational Agent(s)*]_

*Agent not supplied by CTEP: Please include a comprehensive list of all reported adverse events and any potential risks (such as the toxicities seen with another agent of the same class or risks seen in animals administered this agent) as provided by the manufacturer.*

### 7.1.3 Adverse Event List(s) for Commercial Agent(s)

*For each commercial agent, please provide a list of those adverse events most likely to occur on this study, and refer the reader to the package insert(s) for the comprehensive list of adverse events.*

## 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.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1.1).

- **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 home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 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.

7.3.3 **Expedited Reporting Guidelines**– AdEERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 1 Trials

| Phase 1 Trials | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5[2] |
| | | | | Unexpected | | Expected | | |
| | Unexpected and Expected | Unex-pected | Expected | with Hospitali-zation | without Hospitali-zation | with Hospitali-zation | without Hospitali-zation | Unexpected and Expected |
| **Unrelated Unlikely** | Not Required | Not Required | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days |
| **Possible Probable Definite** | Not Required | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days | 24-Hour; 5 Calendar Days | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days |

[1]**Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
AdEERS 24-hour notification followed by complete report within 5 calendar days for:
Grade 3 unexpected events with hospitalization or prolongation of hospitalization
Grade 4 unexpected events
Grade 5 expected events and unexpected events

[2]Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.
December 15, 2004

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the

- event occurs following treatment with an agent under a CTEP IND.

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

7.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (i.e., AdEERS). The following AEs must be reported through the routine reporting mechanism (Section 7.4):

| CTCAE Category | 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 AML/MDS

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols using the NCI/CTEP Secondary AML/MDS Report Form. This form can be downloaded from the CTEP Web site (http://ctep.cancer.gov). Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (available at http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

# 8. PHARMACEUTICAL INFORMATION

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

## 8.1 *CTEP-Supplied Investigational Agent(s)*

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

### 8.1.1 CTEP IND Agent #1 (NSC #)

*Insert pharmaceutical information for CTEP IND Agent #1 here.*

**Availability**

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

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

*CTEP IND Agent #1* is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

### 8.1.2 CTEP IND Agent #2 (NSC #)

*Insert pharmaceutical information for CTEP IND Agent #2 here. If only a single CTEP IND Agent will be used in the trial, this section should be marked "N/A" and the text below deleted.*

**Availability**

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

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

*CTEP IND Agent #2* is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

### 8.1.3 Agent Ordering

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.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and faxing it 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 anytime.

### 8.1.4 **Agent Accountability**

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 CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

## 8.2 ***Other Investigational Agent(s)***

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

*A separate pharmaceutical section is needed for each investigational agent containing at least the following information, available from the appropriate investigator's brochure:*

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

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

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

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

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

8.3 ***Commercial Agent(s)***

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

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

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

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

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

## 9. CORRELATIVE/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).* ***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). 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 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

## 9.2 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 Study[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *CTEP IND Agent* | | A | | | A | | | A | | | A | | | |
| *Other Agent(s)* | | B | B | | B | B | | B | B | | B | B | | |
| 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 |
| Performance status | 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 chemistry[a] | X | X | X | X | X | X | X | X | X | X | 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[c] |
| Radiologic evaluation | X | Radiologic measurements should be performed every *[# weeks]* weeks. | | | | | | | | | | | | X[c] |
| B-HCG | X[b] | | | | | | | | | | | | | |
| *Other tests, as appropriate* | | | | | | | | | | | | | | |
| *Other correlative studies* | | | | | | | | | | | | | | |

A: *CTEP IND Agent*: Dose as assigned; *administration schedule*
B: *Other Agent(s)*: 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.

## 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 *[Agent Name]*.

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, as ≥10 mm with CT scan, or ≥10 mm with 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 lesions Clinical 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-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm 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:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b) 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.
c) 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

#### 11.1.4.1 Evaluation of Target Lesions

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

| | |
|---|---|
| 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).<br><br>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).

11.1.4.3 Evaluation of Best Overall Response

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

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

| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Overall Response when Confirmation is Required*** |
|---|---|---|---|---|
| CR | CR | No | CR | ≥4 wks. Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | documented at least once ≥4 wks. from baseline** |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

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).

### 12.1 Data Reporting

#### 12.1.1 Method

*Please use the appropriate text below, if known.*

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).

*OR*

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm).

**Note**: **All** adverse events that have occurred on the study, including those reported through AdEERS, must be reported via the monitoring method identified above.

#### 12.1.2. 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.*

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center quarterly by *(date for Q1 data)*, *(date for Q2 data)*, *(date for Q3 data)*, and *(date for Q4 data)* to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.1.1.). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

## 12.2 CTEP Multicenter Guidelines

*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.*

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. 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) except for Group studies.

## 12.3 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, Agent-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/industry) 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 investigational 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 investigational 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 NIH, 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 investigational 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 investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. 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 CFR 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:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: 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/Endpoints

*Please specify the study design and primary endpoints. Include information on how toxicity will be graded and reported, and state that all patients who receive any amount of the study drug will be evaluable for toxicity. Precisely define the dose escalation scheme and MTD definition (or refer to the section where they are*

*defined). Accelerated escalation designs with intrapatient dose escalation are encouraged. An example can be found on the following Web site (http://linus.nci.nih.gov/~brb/Methodologic.htm). If an optimal biologic dose will be determined in place of or in addition to the MTD, precisely define how this will be done.*

### 13.2 Sample Size/Accrual Rate

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

### 13.3 Stratification Factors

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

### 13.4 Analysis of Secondary Endpoints

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

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

## REFERENCES

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

# Informed Consent Template for Cancer Treatment Trials

*** NOTES FOR INFORMED CONSENT AUTHORS:**

- 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.
- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- 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'.
- 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/.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- 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.
- 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".]*

## Why is this study being done?

**The purpose of this study is to….** *[Limit explanation to why study is being done. Include a brief explanation of the mechanism of action of the study agent in lay language and why an agent with this mechanism is being studied in this kind of cancer. Explain in 1-3 sentences. Some examples are provided.]*

*[Example: Phase 1 study]*

*Test the safety of [drug/intervention] at different dose levels. We want to find out what effects, good and/or bad, it has on you and your [specify type/stage/presentation of] cancer.*

*[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 this [***type/stage/presentation of cancer***].**

## 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.**

- *[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.**

- *[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.**

- *[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.**

- *[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 dose-finding studies:]* **You will be treated with a dose of the drugs that your doctor thinks is safe for you. Not all patients will get the same doses of the drugs. At the beginning of the study, a few patients will be treated with low doses of the drugs. If these doses do not cause bad side effects, the doses will slowly be made higher for new patients who take part in the study.**

*[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***

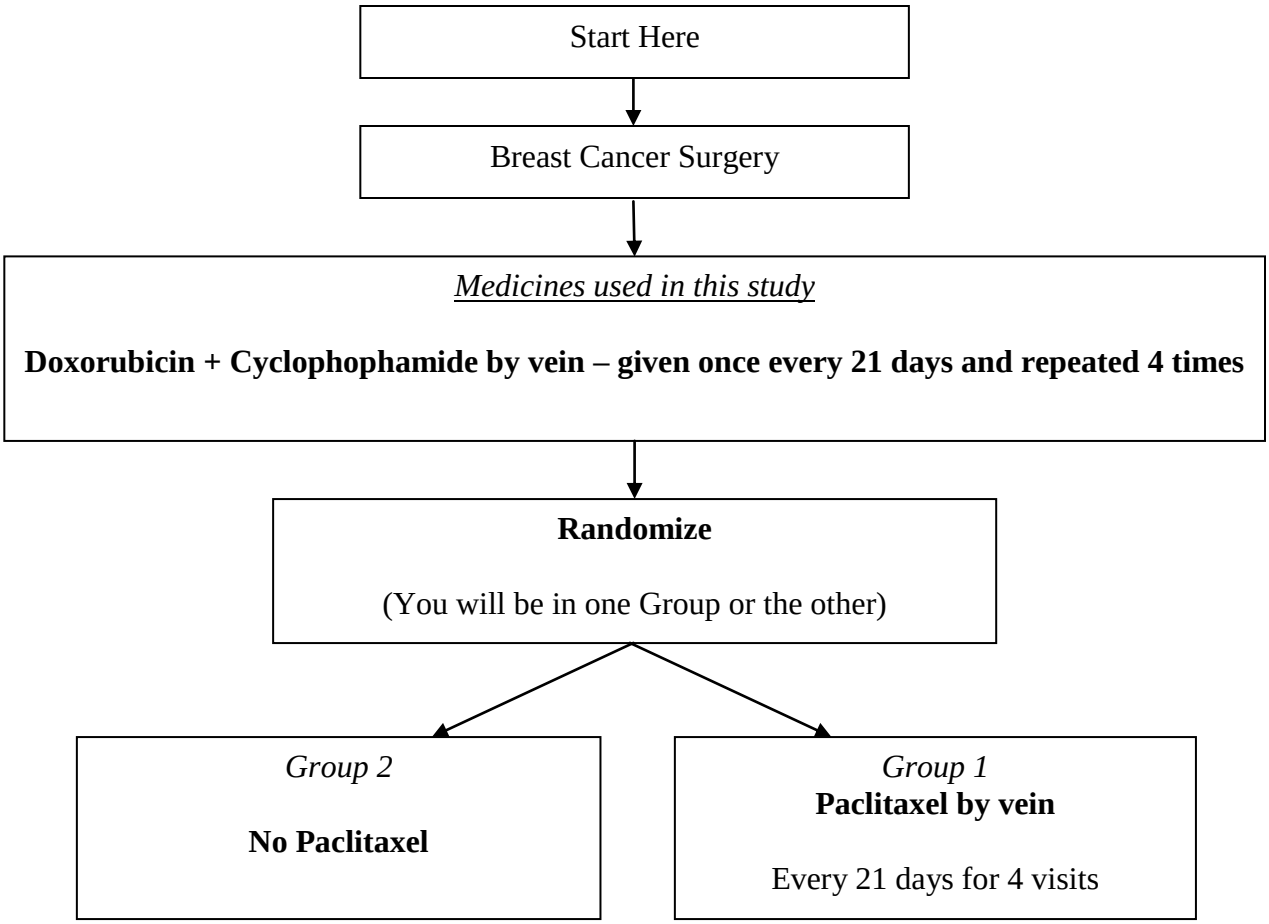
| *Day* | *What you do* |
|---|---|
| Two days before starting study | • Get routine blood tests. |
| Day before starting study | • Check-in to _____ the evening before starting study. |
| Day 1 | • Begin taking _____ once a day. Keep taking _____ until the end of study, unless told to stop by your health care team. |
| Day 2 | • Leave _____ and go to where you are staying. |
| Day 8 | • Get routine blood tests. |
| Day 15 | • Get routine blood tests. |
| Day 22 | • Get routine blood tests. |
| Day 28 | • Get routine blood tests and exams.<br>• Get 2nd chest x-ray for research purposes. |
| Day 29 | • 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 | • 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.<br>• Get routine blood tests each week (more if your doctor tells you to).<br>• Get routine blood tests and exams every cycle (more if your doctor tells you to).<br>• Get routine X-rays, CT scans, or MRIs every other cycle (more if your doctor tells you to). |
| Day 29 | • 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.**



## 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 follow up 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, and devices]* **include those which are:**

**<u>Likely</u>**

- 
- 

- 

**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.*
- *The possibility that unanticipated (or currently unknown) or exacerbated adverse events could occur with the combined study agents because they form a new or untested combination should be noted.*
- *If available, CAEPR (Comprehensive Adverse Events and Potential Risks) document(s) should be used to determine the risks and side effects that should be included in the consent. These side effects should be presented in layman's terms. Consent form authors should contact AdEERSMD@tech-res.com to obtain CAEPRs (if available) for the study agent(s).*
- *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 are 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** *[procedures, drugs, interventions, devices]* **as a treatment for cancer. 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), 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**
- **Pharmaceutical Collaborator** *[This generic language is consistent with the "Standard Protocol Language", and allows for any potential changes in company designations. Please do not specify the name of the company.]*

*[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. 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/specimens/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)** or **TTY: 1-800-332-8615**

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

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to 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

### Performance Status Criteria

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

## APPENDIX B

## 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.