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CHILDREN'S ONCOLOGY GROUP

ADVL1515

A PHASE 1 STUDY OF LY2606368 (prexasertib mesylate monohydrate) ([redacted]), A CHK1/2 INHIBITOR, IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS, INCLUDING CNS TUMORS

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

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[redacted]

For COG PEP-CTN Operations Contacts see: http://members.childrensoncologygroup.org

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For PEP-CTN Operations and Data/Statistics Contacts see:
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AGENT NSC# AND IND#'s

Agent Supplied by Eli Lilly & Co.:
LY2606368 (NSC# 789570, [redacted])

IND Sponsor: COG

SEE SECTIONS 8.3.6, 8.4.2 AND 8.5.6 FOR SPECIMEN SHIPPING ADDRESSES

This trial is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

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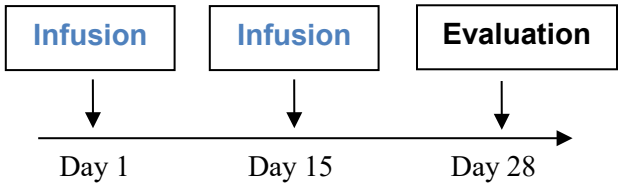
ABSTRACT

In response to DNA damage or replication stress, cells initiate a DNA damage response (DDR) that activates cell cycle checkpoints to halt progress through the cell cycle to allow for DNA repair. DNA damage can arise from normal metabolic processes within the cell (e.g. replication stress) as well as from external sources such as environmental insults (e.g. UV radiation) and DNA-damaging agents.

Checkpoint kinase proteins 1 (CHK1) and 2 (CHK2) are conserved serine/threonine kinases that are key effectors of multiple checkpoint responses in eukaryotic cells exposed to genotoxic stress. CHK1 has also been determined to directly affect repair of DNA, confirming its role in maintaining genomic integrity. Inhibition of CHK1 abrogates the DDR checkpoint, allowing cells that have sustained DNA damage to prematurely enter mitosis and undergo mitotic catastrophe due to incompletely replicated chromosomes. LY2606368 is a novel, second generation selective, dual inhibitor of CHK1/2. In vitro studies focused in cell lines derived from human pediatric tumors (ALL, Ewing's sarcoma, medulloblastoma, neuroblastoma, osteosarcoma, retinoblastoma and rhabdomyosarcoma) indicate that LY2606368 is a potent inhibitor of cell proliferation. Additionally, the antitumor activity of LY2606368 has been evaluated in 14 pediatric tumor xenograft models. LY2606368 was well tolerated and an objective response was noted in 6 of 14 (43%) solid tumor xenografts including neuroblastoma, rhabdomyosarcoma (n=3), Ewing sarcoma, and desmoplastic small round cell tumor (DSRCT). An adult phase I trial in women with breast or ovarian cancer and patients with advanced solid tumors showed that LY2606368 is generally well-tolerated with common side effects of neutropenia, thrombocytopenia, fatigue, nausea, headache, diarrhea, and anorexia. We will conduct a phase 1 trial of LY2606368 in children with relapsed/refractory solid tumors, including CNS, using the rolling six design. The primary aims of this trial will be to establish the maximum tolerated dose of LY2606368 and to characterize the toxicities and pharmacokinetics of LY2606368 in children with these tumors. Our secondary aims will be to preliminarily define the anti-tumor efficacy of LY2606368 within the confines of a phase I trial and to examine CHK1/2 expression status in archival tumor tissue. Additional exploratory aims will seek to define new pharmacodynamic markers of LY2606368 activity by evaluating tumor tissue for deletion and/or mutation of *TP53* and peripheral blood mononuclear cells for autophosphorylation of Chk1 and H2AX.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table	
Cycles- 28 day duration	**Agent**
	**LY2606368 intravenous infusion over 60 minutes**

Treatment will be discontinued if there is evidence of progressive disease or drug-related dose-limiting toxicity that requires removal from therapy. Patients with stable disease or greater response may continue receiving protocol therapy provided that the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy or off study criteria (Section 10.0).

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose of LY2606368 administered as an IV infusion over 60 minutes, every 14 days of a 28-day cycle to children with recurrent or refractory solid tumors.

1.1.2 To define and describe the toxicities of LY2606368 administered on this schedule.

1.1.3 To characterize the pharmacokinetics of LY2606368 in children with recurrent or refractory cancer.

1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of LY2606368 within the confines of a Phase 1 study.

1.2.2 To examine CHK1/2 expression status in archival tumor tissue from solid tumor pediatric patients using immunohistochemistry.

1.2.3 To evaluate tumor tissue for deletion and/or mutation of *TP53* as a potential biomarker of Chk1 inhibition.

1.2.4 To evaluate autophosphorylation of Chk1 and H2AX in peripheral blood mononuclear cells as a potential pharmacodynamic marker of LY2606368 activity.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Genetic material within a cell is exposed to endogenous as well as exogenous sources of stress. Continuous monitoring and maintenance of genetic structure is essential for cell survival and proliferation. In response to DNA damage or replication stress, cells initiate a DNA damage response (DDR) that activates cell cycle checkpoints to halt progress through the cell cycle to allow for DNA repair.[1] DNA damage can arise from normal metabolic processes within the cell (e.g. replication stress) as well as from external sources such as environmental insults (e.g. UV radiation) and DNA-damaging agents.[2] There are primary checkpoints that mediate cell cycle progression – G1/S, S and G2/M that induce cell cycle arrest and allow for DNA damage repair prior to replication or mitosis.[3-5]

Checkpoint kinase proteins 1 (CHK1) and 2 (CHK2) are conserved serine/threonine kinases and are key effectors of multiple checkpoint responses in eukaryotic cells exposed to genotoxic stress. CHK1 is activated by DNA damaging agents like chemotherapy and plays a key role in the intra-S and G2/M DNA damage checkpoints that slow DNA replication and limit mitotic entry, respectively.[6,7] CHK1 is also critical to enforcing the S/M checkpoint when DNA synthesis is blocked and replication is incomplete.[8,9]

CHK1 has also been determined to directly affect repair of DNA, confirming its role in maintaining genomic integrity. Inhibition of CHK1 abrogates the DDR checkpoint, allowing cells that have sustained DNA damage to prematurely enter mitosis and undergo mitotic catastrophe due to incompletely replicated chromosome.[3,10] While the mechanism

of cell death is not well elucidated, it appears that CHK1 inhibitors may be most effective in cells that have a level of DNA damage and/or replication stress.[2,11] In most cases, the level of DNA damage within a tumor cell was the most consistent indicator of drug sensitivity to CHK1 inhibitor. These data suggest that CHK inhibitors would be beneficial therapeutic agents in MYC-driven cancers. Preclinical evidence suggests that targeting intracellular regulation of the cell cycle may be useful in treating tumors such as melanoma that respond poorly to traditional chemotherapeutic agents.[12] Inhibitors of CHK can act in a synthetically lethal manner in cancers with replication stress as a result of these cancers being reliant on CHK proteins for an effective DDR and cell survival.

In normal cell cycle progression, CHK1 prevents the activation of late-stage origins until near the end of S phase and stabilizes active replication forks. Inhibition of CHK1 results in an increased number of active replication origins, which results in stalled replication forks and DNA strand breakage.[6,13,14] Cells deficient in CHK1 have increased spontaneous chromosome missegregation. These cells lose the ability to recruit spindle checkpoint proteins to kinetochores and fail to activate the spindle checkpoint in response to misaligned chromosomes.[5] This finding suggests that CHK1 is essential for stable attachment of mitotic spindles to metaphase chromosomes. Thus, it is postulated that CHK1 inhibition alone can generate DNA damage and induce mitotic catastrophe.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

LY2606368 is a novel, second generation ATP-competitive, selective, dual inhibitor of CHK1/2 that has shown activity in xenograft models of ovarian and prostate cancer as a single agent, as well as in combination with cisplatin or paclitaxel.[15,16] CHK1 inhibition has been reported potentiate the activity of DNA-damaging agents such as cisplatin by exacerbating the cellular DNA damage and reducing the cell's capacity to repair the damage.[17,18] When used as a single agent, LY2606368 causes double-stranded DNA breakage while also removing the protection of the DNA damage checkpoints. Inhibition of CHK1 results in an increase in CDC25A activation of CDK2. The cellular consequences are stalled replication forks, an increase in DNA strand breaks, and replication catastrophe.[6,13,19] Treatment of cells with LY2606368 results in the rapid appearance of TUNEL and pH2AX-positive double-stranded DNA breaks in cells in the S-phase of the cell cycle.[19] In this regard, CHK1 functions as a negative regulator of replication origin activation; specifically, keeping replication origins silent until late S phase. When CHK1 protein is depleted, more replication origins are activated in early S phase than the replication apparatus can tolerate, resulting in slowed and arrested DNA replication forks and DNA double-strand breakage. Treatment with LY2606368 causes a cellular phenotype identical to that reported in ribonucleic acid (RNA) interference (RNAi) knockdown experiments such that HeLa cells treated with LY2606368 show a clear defect in chromatin condensation and failure of the mitotic spindle to attach to chromosomes.[20] These data suggest that as a single agent in vitro, LY2606368 behaves mechanistically as a DNA-damaging agent, a checkpoint inhibitor, and as an inhibitor of DNA replication and mitosis.

Additional *in vitro* studies focused in cell lines derived from human pediatric tumors (ALL, Ewing's sarcoma, medulloblastoma, neuroblastoma, osteosarcoma,

retinoblastoma and rhabdomyosarcoma) indicate that LY2606368 is a potent inhibitor of cell proliferation. In particular, all of the 19 pediatric cell lines tested were highly sensitive to LY2606368 such that the IC_{50} values for growth inhibition were 1 nM or lower.[21] Notably, LY2606368 was more potent than most other agents evaluated which included vincristine, cisplatin, doxorubicin and gemcitabine. There were only 3 situations wherein LY2606368 did not show greater potency that the other single agents and, in these cases LY2606368 showed equivalent, but not lower potency to one of the other 4 agents tested.

The antitumor activity of LY2606368 has been evaluated in 14 pediatric tumor xenograft models.[22] LY2606368 was well tolerated and all models were considered evaluable; an objective response was noted in 6 of 14 (43%) solid tumor xenografts. The models showing regression include neuroblastoma and rhabdomyosarcoma (n=3), Ewing sarcoma and desmoplastic small round cell tumor (DSRCT). Xenograft models showing either disease stabilization or no antitumor effect include osteosarcoma (n=4), retinoblastoma, rhabdomyosarcoma and Ewing sarcoma. Neuroblastoma cells are more sensitive to depletion or inhibition of CHK1 as compared to normal controls, and sensitivity correlates with expression of the oncogene N-MYC and elevated levels of phospho-CHK1.[23]

The preclinical rationale for a study in pediatrics is compelling given the robust antitumor activity of LY2606368 in murine xenograft models of several pediatric tumors.

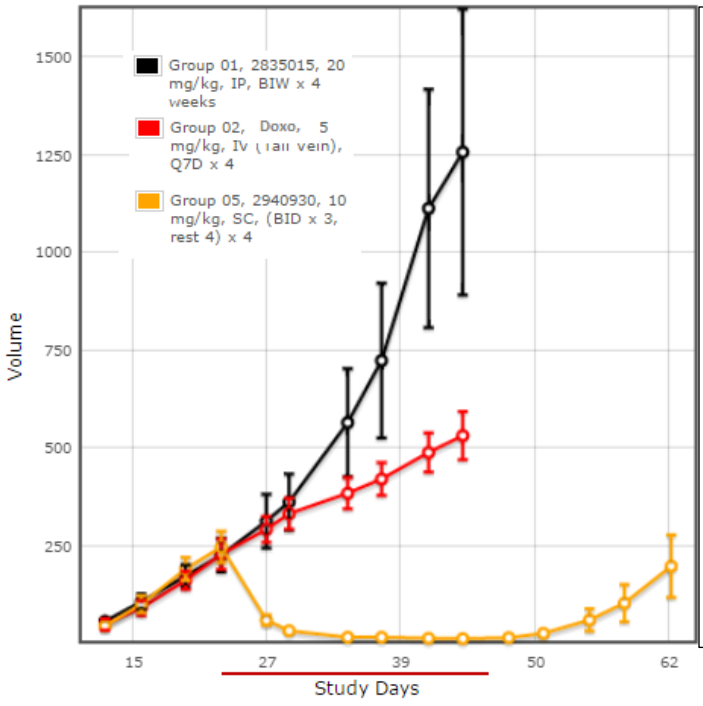


Figure 1: LY2606368 monotherapy in a cell line-derived alveolar rhabdomyosarcoma xenograft model. Athymic nude mice bearing an alveolar rhabdomyosarcoma SJCRH-30 xenograft were treated with vehicle (2835015), doxorubicin or LY2606368 methanesulfonate hydrate ("2940930") beginning on day 24 after average tumor size reached ~ 200 mm^3. LY2606368 at a dose of 10 mg/kg was given during each weekly cycle by subcutaneous injection (SC) twice-daily (BID, at 12-hour intervals) for 3 consecutive days followed by 4 days without dosing for a total of 4 weeks (BIDx3, rest4) x 4. The red bar just below the X-axis illustrates the dosing period. Tumor volume measurements were taken during the course of the study and are plotted versus days following tumor cell implantation.

(Courtesy of Louis Stancato, Richard Beckman, Eli Lilly and Company)

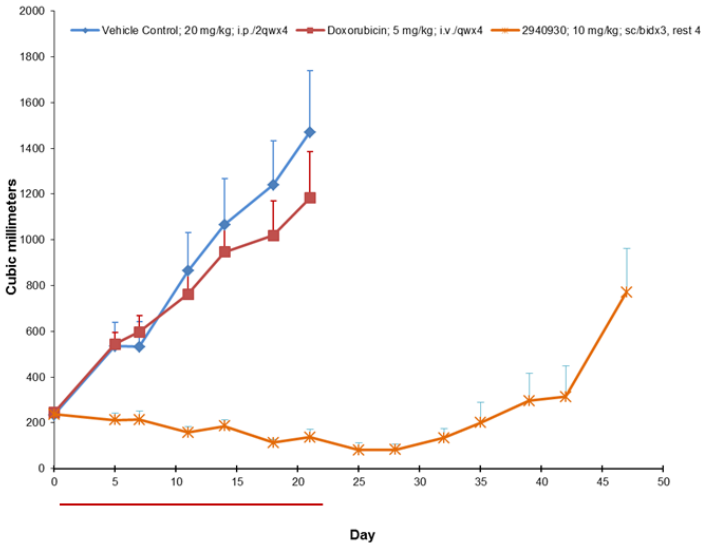


Figure 2: LY2606368 monotherapy in a patient-derived Ewing's sarcoma xenograft model. Athymic nude mice bearing an Ewing's sarcoma PDX model CTG-1094 were treated with vehicle, doxorubicin or LY2606368 methanesulfonate hydrate ("2940930") beginning on day 24 after average tumor size reached ~ 200 mm^3. LY2606368 at a dose of 10 mg/kg was given during each weekly cycle by subcutaneous injection (SC) twice-daily (BID, at 12-hour intervals) for 3 consecutive days followed by 4 days without dosing for a total of 4 weeks (BIDx3, rest4) x 4. The red bar just below the X-axis illustrates the dosing period. Tumor volume measurements were taken during the course of the study and are plotted versus days following tumor cell implantation.

(Courtesy of Louis Stancato, Richard Beckman, Eli Lilly and Company)

2.2.2 Animal Toxicology

Preclinical studies in rats and dogs demonstrated treatment-related findings associated with LY2606368 were generally similar to those of a cytotoxic chemotherapeutic agent, with dose-limiting effects primarily related to bone marrow suppression and GI injury. These effects were dose-dependent. The hematologic effects have also been shown to be schedule-dependent. In rats, treatment-related neutropenia was schedule-dependent, with more severe effects associated with 3 consecutive days per week followed by 14 day recovery period, compared with a single dose the first week. Important effects on cardiovascular function consisting of increased heart rate and decreased blood pressure were attributed to LY2606368 in dogs. On the basis of these collective studies in animals, the dose- limiting toxicity in humans was expected to be 1 or more of the following: myelosuppression, gastrointestinal (GI) toxicity, tachycardia, and hypotension. Patients receiving LY2606368 were closely monitored for these potential effects.[21]

2.2.3 Preclinical Pharmacokinetic Studies

2.2.3.1 Single dose studies in dogs.

The PK of LY2606368 and LY2606368-derived radioactivity were evaluated in rats and dogs following an IV administration of [^{14}C]LY2606368. Concentrations of LY2606368 declined rapidly in a monoexponential fashion following a single 1-hour IV infusion of [^{14}C]LY2606368 in both rats and dogs. At C_{max}, LY2606368 accounted for approximately 37% and 69% of the plasma radioactivity in rats and dogs, respectively. However, the exposure (area under the plasma concentration-time curve [AUC] from time 0 to infinite time [AUC(0-∞)]) of LY2606368 accounted for approximately 16% and 2% of the radioactivity exposure in plasma in rats and dogs, respectively, indicating the presence

of circulating metabolites. Total radioactivity in plasma was followed by a biexponential decline with a steep alpha phase observed during the first 8 hours post start of infusion, and a relatively longer terminal elimination half-life ($t_{1/2}$) for the residual low levels of radioactivity. Metabolites appear to contribute to the longer $t_{1/2}$ of radioactivity when compared with that of LY2606368.

2.2.3.2 Repeated-dose studies in dogs.

LY2606368 was administered as a 1-hour IV infusion to male and female dogs in doses ranging from 1 to 10 mg/kg/day and as a 2-hour IV infusion to male and female dogs at a dose of 40 mg/kg/day on 3 consecutive days per week for 3 weeks (dosed on Days 1, 2, 3, 8, 9, 10, 15, 16, and 17). Systemic exposures to LY2606368 were similar for male and female animals. No accumulation of LY2606368 in plasma was observed following multiple dosing. The increase in C_{max} and $AUC_{(0-24)}$ was roughly dose proportional on Days 1 and 17.

2.3 Adult Studies

2.3.1 Phase 1 Studies

LY2606368 is a novel, second generation, ATP-competitive selective inhibitor of Chk1/2 dual inhibitor that is in early phase clinical trials in women with breast cancer or ovarian cancer (ClinicalTrials.gov NCT02203513) and in patients with advanced solid tumors. As of 4 April 2016, 210 patients have been exposed to LY2606368 with PK data available from 194 patients from 3 ongoing clinical trials (Study JTJA, Study JTJF and Study JTJK). Study JTJA is the first-in-human Phase 1 evaluation of LY2606368.[21] In addition, the National Cancer Institute is sponsoring a Phase 2 study in patients with breast, ovarian or prostate cancer (NCT0220351).

Neutropenia and febrile neutropenia are the most frequent toxicities in these studies and have been observed at all doses and schedules of LY2606368. Neutrophils counts reached their nadir on day 8 of a cycle and resulted in transient grade 4 neutropenia that was less than 5 days. (IB) Grade 4 neutropenia was observed in 66% of the adult patients treated at 105 mg/m^2 every 2 weeks, and a total of 11% of patients experienced febrile neutropenia that was felt by investigators to be related to LY2606368 therapy. None of the febrile neutropenia events required discontinuation of the study and none were associated with an outcome of death. Other hematologic toxicities included anemia (Grade 4: 0%) and thrombocytopenia (Grade 4: 6%).

The most common non-hematologic treatment related adverse events (AEs) and occurring in >5% of patients treated at 105 mg/m^2 every 14 days were fatigue (25%), nausea (12%), headache (11%), diarrhea (9%) and anorexia (8%). The majority of these events were Grade 1 in severity.

In non-clinical studies, LY2606368 elicited effects on the cardiovascular system of dogs consisting of moderate-to-severe increases in heart rate and minimal decreases in blood pressure. Electrocardiogram (ECG) abnormalities were also observed in dogs and prolongation of the QRS duration and QT intervals were

observed at doses above the nonclinical MTD (>80 mg/m^2). A total of 7 patients (6.9%) had a QT change of >30 msec from baseline. No statistically significant changes from baseline were observed.

2.3.2 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

LY2606368 infused over 1 hour had a half-life ($t_{1/2}$) of 10.5 hours in adults with advanced cancer. The major route of metabolism was by CYP450 and 75% of the metabolite was excreted in the feces and 11% in urine.[21] The LY2606368 exposure increased in a dose-dependent manner across the dose range of 10 to 130 mg/m2 on Day 1 of Cycle 1 across both schedules of administration. The mean t1/2 (range: 8.30 to 18.3 hours) varied across days and cycles of treatment after administration of the recommended Phase II dose (RP2D) of 105 mg/m^2. Moderate- to-large degree of inter-patient PK variability in LY2606368 systemic clearance has also been observed. However, the linear relationship between LY2606368 PK parameters and body surface area (BSA) from Study JTJA indicates that administration of LY2606368 based on BSA is an appropriate dosing paradigm. This is the approach we propose to use in pediatric patients.

While *in vitro* data suggested that drug-drug interactions may be possible when LY62606368 is co-administered with cytochrome P450 (CYP)1A2 and CYP2D6 substrates, minimal potential for drug-drug interactions with either substrates was predicted.

While overexpression of Chk1 in adult non-small cell lung cancer tumor tissue has been correlated with poor prognosis[24], phosphorylation of pChk1(S296) has been proposed as a potential predictive biomarker of CHk1 inhibitor sensitivity in breast cancer.[25] We are proposing to evaluate the immunohistochemical localization of Chk1 as an exploratory aim to determine if this may be feasible in a Phase I pediatric study.

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There have been no pediatric studies of LY2606368.

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

There have been no pediatric studies of LY2606368.

2.5 Overview of Proposed Pediatric Study

We propose a phase 1 study of LY2606368 in pediatric patients with recurrent/refractory solid tumors using a rolling 6 design.[26] Based upon the published preclinical data on the importance of cell cycle checkpoint perturbation in tumor types carrying a variety of molecular lesions, we propose this phase 1 study to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of LY2606368. The starting dose selection is based on data from the adult study and RP2D of 105 mg/m^2 once daily on Days 1 and 15, every 28 days. The initial dose level in pediatric patients will be 80 mg/m^2, which is approximately 80% of the adult RP2D, with one dose de-escalation for toxicity and 3 dose escalations to define the dose in children with refractory/recurrent solid tumors.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Oncology Patient Enrollment Network (OPEN), a web-based registration system available on a 24/7 basis. It is integrated with the NCI Cancer Trials Support Unit (CTSU) Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the RAVE database.

Access requirements for OPEN:
Investigators and site staff will need to be registered with CTEP and have a valid and active Cancer Therapy Evaluation Program-Identity and Access Management (CTEP-IAM) account (check at https://ctepcore.nci.nih.gov/iam/index.). This is the same account (user id and password) used for credentialing in the CTSU members' web site (refer to Appendix X for CTEP and CTSU registration procedures). To perform registrations in OPEN, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:

1. Log in to https://open.ctsu.org/open/
2. Click the **Slot Reservation** Tab. *The Site Patient page opens.*
3. Click the **Report** Tab. *The Slot Reservation Report opens. Available Slots are detailed per study strata.*

3.2 IRB Approval

NCI Pediatric CIRB approval or local IRB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit CIRB/IRB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the Regulatory Tab.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission
When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

For general (non-regulatory) questions, call the CTSU General Helpdesk at: 1-888-823-5923 or contact CTSU by email at ctsucontact@westat.com.

Study centers can check the status of their registration packets by accessing the Site Registration Status page on the CTSU Member's Website under the Regulatory Tab. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

3.3 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry in the OPEN system once authorization for the release of protected health information (PHI) has been obtained.

3.4 Reservation and Contact Requirements

Before enrolling a patient on study, a reservation must be made through the OPEN website and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient ID number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

Reservations may be obtained 24-hours a day through the OPEN website.

3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.6 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through one of the following mechanisms: a) the COG screening protocol, b) an IRB-approved institutional screening protocol or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.7 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.8 Institutional Pathology Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

3.9 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the COG Study Research Coordinator, or the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

3.10 Dose Assignment

The dose level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT), and serum creatinine. If the re-check is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary). For patients whose disease is evaluated with a bone marrow examination, the bone marrow aspirates and biopsies are required within 14 days prior to the start of chemotherapy.

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's

medical or research record which will serve as the source document for verification at the time of audit.

4.1 Inclusion Criteria

4.1.1 Age: Patients must be ≥ than 12 months and ≤ 21 years of age at the time of study enrollment.

4.1.2 Diagnosis: Patients with recurrent or refractory solid tumors, including CNS tumors, are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or in patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG.

4.1.3 Disease Status: Patients must have either measurable or evaluable disease (see Sections 12.2 and 12.3 for definitions).

4.1.4 Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

4.1.5 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). Note: Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.6 Prior Therapy

4.1.6.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the defined eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the Study Chair and the study-assigned Research Coordinator prior to enrollment.
   - ≥ 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).

b. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days must have elapsed from last dose of agent. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed,

the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

d. Corticosteroids: See Section 4.2.2.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

e. Hematopoietic growth factors: ≥ 14 days must have elapsed since the last dose of a long-acting growth factor (e.g. pegfilgrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the Study Chair and the study-assigned Research Coordinator.

f. Interleukins, Interferons and Cytokines (other than Hematopoietic Growth Factors): ≥ 21 days must have elapsed since the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors).

g. Stem cell Infusions (with or without TBI):
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days must have elapsed after infusion, and no evidence of GVHD.
- Autologous stem cell infusion including boost infusion: ≥ 42 days must have elapsed after completion.

h. Cellular Therapy: ≥ 42 days must have elapsed since the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.).

i. XRT/External Beam Irradiation including Protons: ≥ 14 days must have elapsed after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.

j. Radiopharmaceutical therapy (e.g., radiolabeled antibody, ^{131}I-MIBG): ≥ 42 days must have elapsed since systemically administered radiopharmaceutical therapy.

k. Patients must not have received prior exposure to LY2606368.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 75,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Hemoglobin ≥ 8.0 g/dl at baseline (may receive PRBC transfusions)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 patients must be evaluable for hematologic toxicity for the dose-escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function Defined as:
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.1.7.3 Adequate Liver Function Defined as:
- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age regardless of baseline.
- SGPT (ALT) ≤ 135 U/L (3x ULN). For the purpose of this study, the ULN for SGPT is 45 U/L regardless of baseline.
- Serum albumin ≥ 2 g/dL.

4.1.7.4 Adequate Cardiac Function Defined As:
- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by gated radionuclide study
- QTc ≤ 480 msec

Note: Patients should avoid concomitant medication known or suspected to prolong QTc interval or cause Torsades De Pointes. If possible, alternative agents should be considered.
Patients who are receiving drugs that prolong the QTc are eligible if the drug is necessary and no alternatives are available. See Appendix IV for drugs that may prolong the QTc.

4.1.7.5 Adequate Neurologic Function Defined as:

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- Nervous system disorders (CTCAE v5) resulting from prior therapy must be ≤ Grade 2 with the exception of decreased tendon reflex (DTR). Any grade of decreased tendon reflex is eligible.
- For patients with CNS tumors, any baseline neurologic deficit, including seizures, must be stable for at least one week prior to initiating study treatment.

4.1.8 Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.1.9 Tissue blocks or slides must be sent per Section 8.4 if available. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study because there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method both during and for 3 months after participation in this study. Abstinence is an acceptable method of contraception.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving corticosteroids must have been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (See Section 4.1.6.1.d).

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

4.2.2.4 Anti-GVHD agents post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host

disease post bone marrow transplant are not eligible for this trial.

4.2.2.5 Strong CYP1A2 Inhibitors: Patients must not have received strong CYP1A2 inhibitors (ciprofloxacin, fluvoxamine, zafirlukast) for at least 7 days prior to enrollment and must not receive them for the duration of the study.

4.2.2.6 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.2.7 Patients who have received a prior solid organ transplantation are not eligible.

4.2.2.8 Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to LY2606368 or to its formulation are not eligible.

4.2.2.9 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Day 1	Day 15	Day 28
LY2606368 IV	LY2606368 IV	End of Cycle/Evaluation

LY2606368 will be administered intravenously over 60 minutes on Days 1 and 15 of a 28 day cycle. A cycle may be repeated for a total of 13 cycles, up to a total duration of therapy of approximately 12 months.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

Criteria for delaying or omitting the Day 15 dose of LY2606368 are specified in Section 6.1.

Patients should be monitored for signs and symptoms of infusion reactions during LY2606368 administration and for 30 minutes after the flush completion. See Section 6.3.4 for management guidelines for infusion reactions.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0.

5.3 Dose Escalation Schema

5.3.1 Inter-Patient Escalation

The starting dose of LY2606368 will be 80 mg/m^2 (dose level 1) with dose levels for subsequent groups of patients as follows.

Dose Level	LY2606368 **(mg/m^2)**
0	60
1*	**80**
2	100
3	125
4	150

* Starting Dose Level

There will be no escalations beyond dose level 4 (150 mg/m^2), as previous pediatric Phase 1 studies have rarely defined a MTD greater than 160% of the adult MTD.

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 60 mg/m^2 (dose level 0). If dose level 0 is not well tolerated, further de-escalation will not occur. The study will be closed to accrual.

5.3.2 Intra-Patient Escalation

There will not be intra-patient dose escalation.

5.4 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.5 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.5.1 Non-hematological dose-limiting toxicity

5.5.1.1 Any Grade 3 or greater non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea and vomiting < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT, that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L and the ULN for AST is defined as 50 U/L. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See Appendix IX for values that represent thresholds between CTCAE grades.
- Grade 3 fever
- Grade 3 infection

- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.

5.5.1.2 Non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles.

5.5.1.3 Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.5.2 Hematological dose limiting toxicity

5.5.2.1 In patients evaluable for hematological toxicity (see Section 4.1.7.1), hematological dose limiting toxicity is defined as:

- Day 15:
  - Grade 4 neutropenia or Grade 3 thrombocytopenia (platelets < 50,000/mm^3) that does not resolve to ANC ≥ 500/mm^3 and platelets ≥ 50,000/mm^3 (transfusion independent) by Day 18 will be considered dose-limiting (See Section 6.1).
- Grade 4 neutropenia for > 7 days
- Platelet count < 20,000/mm^3 on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7-day period
- Myelosuppression that causes a delay of > 14 days between treatment cycles.

5.5.2.2 Note: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

6.1 Dose Modifications for Day 15 Dosing due to Toxicity on Day 15

6.1.1 Hematologic Toxicity

6.1.1.1 Patients who have Grade 4 neutropenia or Grade 3 thrombocytopenia (platelets < 50,000/mm^3) on Day 15 will have their dose withheld. If the toxicity resolves to ANC ≥ 500/mm^3 and platelets ≥ 50,000/mm^3 (transfusion independent) by Day 18, the dose may be given. If the toxicity does not resolve to ANC ≥ 500/mm^3 and platelets ≥ 50,000/mm^3 by Day 18, the dose will be omitted and this will be considered a DLT. Patients should receive subsequent cycles of drug per Section 6.2. Patients who require that their Day 15 dose be omitted for Grade 4 neutropenia or Grade 3 platelets (< 50,000/mm^3) after two dose reductions must be removed from protocol therapy.

6.1.1.2 Patients who meet hematological DLT criteria as defined in Section 5.5.2.1 on Day 15 will have their Day 15 dose omitted. Patients should receive subsequent cycles of drug per Section 6.2 after their toxicity resolves, no sooner than the planned start of the subsequent cycle. Patients

who require that their Day 15 dose be omitted for hematologic DLT as defined in Section 5.5.2.1 after two dose reductions must be removed from protocol therapy.

6.1.2 Non-Hematologic Toxicity

6.1.2.1 Patients who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug **prior to** the Day 15 dose (with the exception of the DLT exclusions in Section 5.5.1.1) will be considered to have had a DLT. If the toxicity resolves to meet eligibility or ≤ Grade 2 (if not part of eligibility criteria) by Day 15, the dose may be given but at the next lower dose level.

6.1.2.2 Patients who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug **on** Day 15 prior to dosing (with the exception of the DLT exclusions in Section 5.5.1.1) will have their dose withheld and this will be considered a DLT. If the toxicity resolves to meet eligibility or ≤ Grade 2 (if not part of eligibility criteria) by Day 18, the dose may be given but at the next lower dose level. If the toxicity does not resolve by Day 18, the dose will be omitted. Patients should receive subsequent cycles of drug but with dose modifications according to Section 6.3.

6.2 Dose Modifications for Hematological Toxicity

6.2.1 Patients who have dose-limiting thrombocytopenia should receive subsequent cycles at the next lower dose level.

6.2.2 Patients who have dose-limiting neutropenia with no other dose-limiting toxicity should receive the same dose in the next cycle with myeloid growth factor support. [Note: Patients MUST NOT receive prophylactic myeloid growth factor in the first cycle of therapy (See Section 7.4).] If dose-limiting neutropenia recurs after myeloid growth factor is added, then the patient should be given the next lower dose level for subsequent cycles. If dose-limiting neutropenia recurs in a patient that has received a dose level reduction but has not received myeloid growth factor, then myeloid growth factor should be administered. Patients who experience dose-limiting neutropenia after the addition of myeloid growth factor and one dose reduction must be removed from protocol therapy.

6.2.3 Patients who meet hematological DLT criteria as defined in Section 5.5.2.1 on Day 15 and have their Day 15 dose omitted will begin the subsequent cycle at the planned start of that cycle, if their toxicity has resolved.

6.2.4 Patients who experience dose-limiting thrombocytopenia after two dose reductions or dose-limiting neutropenia after addition of myeloid growth factor and one dose reduction must be removed from protocol therapy.

6.2.5 Patients who have a dose-limiting hematological toxicity that does not resolve to eligibility parameters within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.2.6 No dose reduction beyond dose level 0 is allowed.

6.3 Dose Modifications for Non-Hematological Toxicity

6.3.1 Patients who have any dose-limiting non-hematological toxicity (as defined in Section 5.5.1) may continue on protocol therapy upon meeting eligibility lab requirements or baseline but should receive subsequent doses at the next lower dose level.

6.3.2 If the same non-hematological dose-limiting toxicity recurs after one dose reduction, the patient must be removed from protocol therapy.

6.3.3 Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or eligibility within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.3.4 No dose reduction beyond dose level 0 is allowed.

6.3.5 Infusion Reactions: Patients experiencing an infusion reaction should be treated as per institutional guidelines. For subsequent infusions, premedication with diphenhydramine 0.5-1 mg/kg (max 50 mg) and/or other premedications may be considered at investigators discretion. The infusion rate may also be decreased by 50%. Patients should be monitored for signs and symptoms of infusion reactions with subsequent infusions.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See Section 4.2.2.5 for drugs that should not be used concomitantly due to potential interactions with LY2606368. Drugs that prolong the QTc may be used only if the drug is necessary and no alternatives are available. See Appendix IV for drugs that may prolong the QTc.

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered in accordance with Section 6.2.2 or for culture proven bacteremia or invasive fungal infection. G-CSF may be used only after completion of cycle 1 and may be given 24 hours after the administration of the dose on day 1 and day 15. G-CSF administration must be stopped 7 days prior to initiation of the subsequent cycle.
The Study Chair should be notified before growth factors are initiated.

7.5 Concomitant Medications

7.5.1 Drugs that prolong the QTc may be used only if the drug is necessary and no alternatives are available. See Appendix IV for drugs that may prolong the QTc.

7.5.2 Sensitive CYP1A2 substrates (alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine) may be used, but should be recorded as concomitant medications.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Neurologic Exam	X		X
Height, weight, BSA	X		X
Performance Status	X		
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[3]	Weekly[4]
Pharmacokinetics[1]	X	X	
Electrolytes including Ca^{2+}, PO_4^{3-}, Mg^{2+}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X		X
Tumor Disease Evaluation	X	End of Cycle 1	Every other cycle x 2 then q 3 cycles [5]
Bone Marrow Evaluation[6]	X	X	Every other cycle x 2 then q 3 cycles[6]
Pregnancy Test[2]	X		
ECHO or gated radionuclide study	X		
EKG[9]	X	X	X[9]
Tumor Tissue Submission[7]	X		
Correlative Biology Studies (optional)[8]	X	X	

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle, unless otherwise specified within the table.

1 See Section 8.3 for timing and details of pharmacokinetic (PK) studies.

2 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control during the study and for 3 months after participation in this study. Abstinence is an acceptable method of birth control.

3 If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose-limiting toxicity.

4 If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3

5 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

6 If a solid tumor patient is suspected to have or has a history of bone marrow involvement then a pre-study bone marrow biopsy and/or aspirate is required. This should then be repeated with each tumor disease evaluation.

7 See Section 8.4 for details regarding tumor tissue submission for the required and optional studies. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment.

8 See Section 8.5 for timing and details regarding correlative biology studies.

9 EKGs to be performed at baseline, and then immediately prior to and one hour after each infusion of LY2606368 is complete for the first 2 cycles. For subsequent cycles, EKGs are to be obtained as clinically indicated.

8.2 Radiology Studies

Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy will be centrally reviewed. COG Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the treating institution forward the requested images for central review. The central image evaluation results will be entered into RAVE for review by the COG Operations Center and for data analysis.

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the ImageInBox.

COG institutions that are not connected via the ImageInBox can send the images on CD ROM or USB flash drive. Submitted imaging studies should be clearly marked with the COG patient ID, study number (STUDY #ADVL1515) and date and shipped to Syed Aamer at the address below:

Syed Aamer, MBBS, CRP
Administrator, Imaging Research Center
Children's Hospital Los Angeles
4650 Sunset Boulevard, MS # 81
Los Angeles, CA 90027
Phone: (323) 361-3898
Fax: (323) 361-3054
E-mail: saamer@chla.usc.edu

8.3 Pharmacology

8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of LY2606368 in children. Plasma will be collected and LY2606368 concentrations will be determined by a validated LC/MS/MS method. Samples will be analyzed by Covance Laboratories.

8.3.2 Sampling Schedule (See Appendix V)

Blood samples will be obtained at the following time points:
Day 1: pre-dose, and at 1 (end of infusion), 1.5, 2, 4, and 8 hours after beginning the infusion.
Day 2: 24 hrs. (± 2 hrs.) after beginning the infusion.
Day 5 (± 1): 96 hrs. (± 24 hrs.) after beginning the infusion.
Day 8: During CBC evaluation
Day 15: pre-dose and end of infusion (1 hour after beginning the infusion).

8.3.3 Sample Collection and Handling Instructions

Blood samples (2 -3 ml) will be collected in K^2EDTA or K^3EDTA tubes at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact start and stop time of the infusion.

8.3.4 Sample Processing

1. Invert the tube gently at least 8 to 10 times to ensure mixing of the K^2EDTA or K^3EDTA and blood.
2. Immediately after collection place K^2EDTA or K^3EDTA tube on ice or at 4°C for no longer than 30 minutes.
3. Centrifuge tube within 30 minutes of collection at 2000 g for 10 minutes at 4°C until red cells and plasma are well separated.
4. Transfer the plasma to cryovials. Do not transfer the buffy coat or any of the red cell pellet into the plasma sample as this will render the sample unusable for analysis.
5. Immediately after transfer of the plasma to cryovials, freeze the plasma samples on dry ice, snapfreeze in liquid nitrogen, or place directly into a -70°C freezer.
6. Store in -70°C freezer until shipment.

8.3.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

8.3.6 Sample Shipping Instructions

Samples should be stored at -70°C until shipping, batched per patient and shipped frozen on dry ice in opaque containers at the end of Cycle 1. Shipments should only be sent out on Monday through Thursday via Fedex priority overnight to the following address:

Covance Bioanalytical Laboratory Services Inc.
3301 Kinsman Boulevard
Madison, WI 53704-2523
Attn: Sample Management – Bioanalytical (Rm131D 1S)

Call the Covance Bioanalytical Services Sample Management department on the day prior to shipment (1-888-541-7377 Ext 2540, Ext 2187, or Ext 2327), as notification of the intended shipment, or e-mail madison.SA@covance.com with shipment information (tracking numbers and number of boxes to be sent).

Please note the Covance study #8366627 for this study.

For further guidance, please see the sample shipping guidelines provided by Covance attached to the memo dated July 4th 2017.

8.4 Tissue Studies (required)

Archival tumor tissue should be submitted for all patients. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

8.4.1 Description of Studies

8.4.1.1 CHK 1/2 Expression

Tissue will be collected either from diagnosis or relapse to evaluate CHK1/2 expression in pediatric solid tumors prior to treatment with LY2606368. Tumor tissue will be analyzed by immunohistochemistry.

8.4.1.2 *TP53* Deletion/Mutation

Tissue will be collected either from diagnosis or relapse to evaluate for a deletion and/or mutation of *TP53* by immunohistochemistry and/or sequencing.

8.4.2 Sample Collection, Handling, and Shipment

Paraffin-embedded tissue blocks or slides will be shipped to Dr. Cynthia Wetmore at Phoenix Children's Hospital. Detailed instructions regarding collection, handling, and shipping of tissue samples are located in Appendix VI.

8.4.3 Sample Labeling

Each sample must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was taken. Data should be recorded on the Tissue Study Form, which must accompany the sample(s).

8.5 Correlative Biology Studies (optional)

8.5.1 Description of Studies

Peripheral blood mononuclear cells (PBMCs) will be evaluated in consenting patients for autophosphorylation of Chk1 and H2AX using immunohistochemistry and/or phospho-flow cytometry.

8.5.2 Sampling Schedule (See Appendix VII)

Blood samples (5 ml) will be collected at baseline prior to infusion and at 24 hours after start of infusion (at time of PK sample collection).

8.5.3 Sample Collection and Handling Instructions

Blood samples (5 ml) will be collected in CPT tubes at a site distant from the infusion for pharmacodynamic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug was administered.

8.5.4 Sample Processing

Instructions for isolating PBMCs can be found in Appendix VIII. PBMCs should be kept on ice or refrigerated and processed within 1 hour of collection. Samples should be frozen standing upright in a rack or box to ensure that samples do not freeze to the sides and cap of the tube. Whenever possible, sites should use standard cryovials (i.e. volumes ≤ 2.0 mL) that can fit in a standard 81-place freezer box.

8.5.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., the date and time the sample was drawn, and the type of sample (either PMBC or plasma). Data should be recorded on the Correlative Study Form, which must accompany the sample(s).

8.5.6 Sample Shipping Instructions

Samples should only be sent between Monday and Wednesday to ensure that sample shipments arrive at the lab during the work week. Please send an email confirmation prior to shipment to CCTDC@emory.edu while copying the study specific research coordinator. This email should include the patient ID, tracking number, and the name of the shipping site.

Frozen samples may be batched and shipped together on dry ice to:

[redacted]

9.0 AGENT INFORMATION

[redacted]

9.1.3 [redacted]

[redacted]

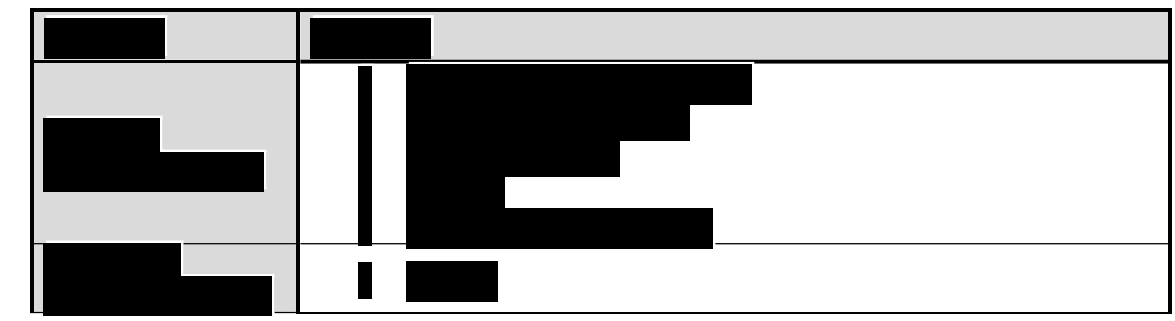
9.1.5 [redacted]

9.1.6 [redacted]

[redacted]

9.1.7 [redacted]

[redacted]



9.2

[redacted]

[redacted]

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0).
b) Adverse Events requiring removal from protocol therapy (See Section 13.0).
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 13 cycles of therapy.
f) Physician determines it is not in the patient's best interest.
g) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of LY2606368 (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up
d) Withdrawal of consent for any required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

A minimum of 4 patients will be enrolled in this study. The expected maximum number of evaluable patients required to estimate the MTD/RP2D is 24. Once the MTD or recommended Phase 2 dose has been defined, up to 6 additional patients with recurrent or refractory solid tumors without restrictions on heme evaluability may be enrolled to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). Therefore, a maximum of 36 patients are expected to be enrolled which allows for 6 patients at each of 4 dose levels, 6 additional patients enrolled at the MTD/RP2D for PK analysis, and a 20% inevaluable rate. Review of the enrollment rate into previous COG new agent studies indicates that 1-2 patients per month are available, which will permit completion of the study within 18-36 months. An absolute maximum of 65 patients is anticipated in the unlikely scenario that each of 4 dose levels is expanded to 12 patients due to different classes of AEs, 6 additional patients are enrolled at the MTD for PK analysis, and a 20% inevaluable rate. The absolute maximum would require about 33-65 months for completion.

11.2 Definitions

11.2.1 Evaluable For Adverse Events

Any patient who receives at least one dose of the study drug(s) and/or who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-escalation portion during Cycle 1, patients must receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. Patients who do not have DLT and are not considered evaluable for toxicity will be replaced.

11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy.

- In the unlikely event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), AND all of the following conditions are met, expansion of the cohort to 12 patients will be considered:

  - One of the DLTs does not appear to be dose-related
  - The Adverse Effects are readily reversible
  - The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

  If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.

- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥ 1/3 of the cohort of patients at the MTD (during the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

11.3 Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study.[26] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	**# Pts with DLT**	**# Pts without DLT**	**# Pts with Data Pending**	***Decision***
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level

2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule).

In addition to determination of the MTD, a descriptive summary of all toxicities will be reported.

11.4 Inclusion of Children, Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

The gender and minority distribution of the study population is projected to be[1]:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	2	0	0	**4**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	7	0	0	**11**
White	16	26	4	3	**49**
More Than One Race	1	0	0	0	**1**
Total	**23**	**35**	**4**	**3**	**65**

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11.5 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of LY2606368 will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to evaluate the toxicity of LY2606368, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors, and will be reported descriptively.

All these analyses will be descriptive and exploratory and hypotheses generating in nature.

[1]These distributions are based on historical Phase 1 enrollments.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

12.2 Response Criteria for Patients with Solid Tumors

See the table in Section 8.0 for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained on the next consecutive cycle following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[27] Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.2.1 Definitions

12.2.1.1 Evaluable for objective response: Patients who exhibit objective disease progression prior to the end of cycle 1 will be considered evaluable for response. For all other patients, 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.

12.2.1.2 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.

12.2.2 Disease Parameters

12.2.2.1 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 must show definitive evidence of progression to be considered measurable.

12.2.2.2 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 no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

12.2.2.3 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.

12.2.2.4 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 that 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.

12.2.2.5 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.

12.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

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.

12.2.3.1 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.

12.2.3.2 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.

12.2.3.3 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). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

12.2.3.4 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.

12.2.3.5 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.

12.2.3.6 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).

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

12.2.3.7 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.

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

12.2.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.2.4.1 **Evaluation of Target Lesions**

Complete Response (CR):	Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).
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). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy

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

12.2.4.2 **Evaluation of Non-Target Lesions**

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

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

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

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

12.2.5 Overall Response Assessment

Table 1: 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	≥ 28 days Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 28 days 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 ≥ 28 days 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.				

** 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.

Table 2: 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		

Table 4: Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	MIBG	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

12.2.6 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.3 Response Criteria for Patients with Solid Tumors and Evaluable Disease

12.3.1 Evaluable Disease

The presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

12.3.2 Complete Response

Disappearance of all evaluable disease.

12.3.3 Partial response

Partial responses cannot be determined in patients with evaluable disease

12.3.4 Stable Disease (SD)

That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

12.3.5 Progressive Disease

The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

12.3.6 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.4.1 MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

12.4.2 The following criteria will be used to report MIBG response by the treating institution:

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

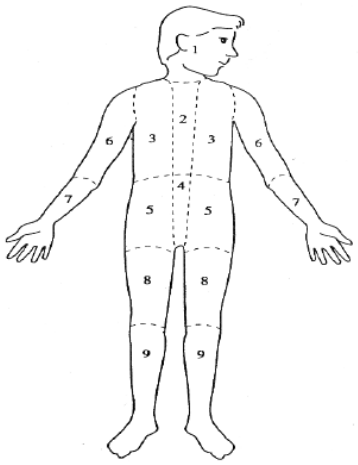
12.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

NOTE: This scoring should also be done by the treating institution for end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan**.** In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,
1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan.

12.4.4 Overall Response Assessment

Table 5: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only

If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

12.4.5 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 3 in Section 12.7.

12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.5.1 Bone Marrow Involvement

Bone marrow obtained within 14 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by H&E Staining of bilateral bone marrow biopsies and aspirates.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

In patients who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 21 days apart.

Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

12.5.2 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Section 12.7.

12.6 Response Criteria for Patients with CNS Tumors

12.6.1 Measurable Disease

Any lesion that is at minimum 10 mm in one dimension on standard MRI or CT, for CNS tumors.

12.6.2 Evaluable Disease

Evaluable disease is defined as at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, CSF cytology, or other reliable measures.

12.6.3 Selection of Target and Non-Target Lesions

For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

Any change in size of non-target lesions should be noted, though does not need to be measured.

12.6.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial response (PR):** ≥ 50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.
- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD.
- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the perpendicular diameters of the target lesions, taking as reference the smallest sum of the products observed since the start of treatment, or the appearance of one or more new lesions.

12.6.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.
- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.
- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

12.6.6 Response criteria for tumor markers (if available):

Tumor markers will be classified simply as being at normal levels or at abnormally high levels.

12.6.7 Overall Response Assessment

The overall response assessment takes into account response in both target and non-target lesions, the appearance of new lesions and normalization of markers (where applicable), according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, marker and new lesions in the preceding columns.

Target Lesions	**Non-target Lesions**	**Markers**	**New Lesions**	**Overall Response**
CR	CR	Normal	No	**CR**
CR	IR/SD	Normal	No	**PR**
CR	CR, IR/SD	Abnormal	No	**PR**
PR	CR, IR/SD	Any	No	**PR**
SD	CR, IR/SD	Any	No	**SD**
PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.7 Best Response

12.7.1 Evaluation of Best Overall Response

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

Table 3. Sequences of overall response assessments with corresponding best response.

1st Assessment	**2nd Assessment**	**Best Response**
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR

PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

12.7.2 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.

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. The descriptions and grading scales found in the revised CTCAE version 5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded

from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Step 2: Grade the adverse event using the NCI CTCAE version 5.0.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- There are any protocol-specific exceptions to the reporting requirements.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found below under the section entitled "Additional Instructions or Exceptions."
Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

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

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

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

- Grade 1 and 2 adverse events listed in the table below do **not** require expedited reporting via CTEP-AERS:

Category	Adverse Events
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Edema (limbs)
GASTROINTESTINAL DISORDERS	Constipation
GASTROINTESTINAL DISORDERS	Diarrhea
GASTROINTESTINAL DISORDERS	Dry mouth
GASTROINTESTINAL DISORDERS	Nausea
GASTROINTESTINAL DISORDERS	Vomiting
GASTROINTESTINAL DISORDERS	Abdominal pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fever
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Neck pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Headache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Febrile Neutropenia
INVESTIGATIONS	Alanine aminotransferase increased
INVESTIGATIONS	Aspartate aminotransferase increased
METABOLISM AND NUTRITION DISORDERS	Anorexia
METABOLISM AND NUTRITION DISORDERS	Dehydration
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Myalgia
NERVOUS SYSTEM DISORDERS	Dizziness
PSYCHIATRIC DISORDERS	Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnea
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash

As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the CTEP Adverse Event Reporting System (CTEP-AERS) that can be found at http://ctep.cancer.gov.
A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.
If prompted to enter a sponsor email address, please use: PEPCTNAERS@childrensoncologygroup.org.
Email supporting documentation to the ADVL1515 COG Research Coordinator.

ALWAYS include the ticket number on all emailed documents.

13.4 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG case report forms and do not alter the guidelines for CTEP-AERS reporting.

13.4.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.4.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.4.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.4.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.4.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2) should be reported at the end of each cycle using the forms provided in the CRF packet (See Section 14.1).

13.5.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry-sponsored trials).

13.5.3 Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

13.6 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP) via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after protocol treatment for cancer.

Secondary Malignancy:

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

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

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

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

Second Malignancy:

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

13.7 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and emailed to the ADVL1515 COG Study Assigned Research Coordinator along with any additional medical information (Appendix III). The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.7.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (Pregnancy)" under the "Pregnancy, puerperium and perinatal conditions" System Organ Class (SOC).

- Pregnancy should be followed until the outcome is known. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

13.7.2 Pregnancy Loss (Fetal Death)

- Pregnancy loss is defined in CTCAE as "Death in utero."

- Any pregnancy loss should be reported expeditiously, as **Grade 4** "Pregnancy loss" under the "**Pregnancy, puerperium and perinatal conditions**" **SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.7.3 Death Neonatal

- Neonatal death, defined in CTCAE as "***Newborn deaths occurring during the first 28 days after birth***" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

- A neonatal death should be reported expeditiously as Grade 4 "Death neonatal" under the "General disorders and administration" SOC **when the death is the result of a patient pregnancy or pregnancy in partners of men on study**.

- Do NOT report a neonatal death resulting from a pregnancy or pregnancy in partners as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. 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 Website (http://ctep.cancer.gov/reporting/cdus.html).

Note: If this study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If this study has been assigned to CDUS-abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CTEP-AERS. This is not a responsibility of institutions participating in this trial.

14.3 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.3.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the PEP-CTN scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG PEP-CTN Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.3.2 Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the COG PEP-CTN Chair, Vice Chair and Statistician on a weekly conference call.

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: CORRELATIVE STUDIES GUIDE

Correlative Study	Appendix	Sample Volume		Tube Type
		Volume per sample	Total Cycle 1	
PK	V	2 - 3 ml	22 -33 ml	EDTA tubes
PBMC	VIII	5 ml	10 ml	CPT tubes
Tumor Tissue (Required) *See Section 8.4 for details*	VI	-	-	-
Total Blood Volume			**32 - 43 ml**	

APPENDIX III: PREGNANCY INFORMATION FORM

Attach to CTEP-AERS 5-Day Report

PREGNANCY INFORMATION FAX
FACSIMILE TRANSMISSION
Ticket Number:_____

Study #:
SAF FAX NO: (301) 230-0159
ALTERNATE FAX NO: (301) 897-7404

Initial Report Date: ___ - ___ - ___ (DD - MMM - YY)	Follow-up Report Date: ___ - ___ - ___ (DD - MMM - YY)
Principal Investigator:	Reporter:
Reporter Telephone #:	Reporter FAX #:

Investigator Number ☐☐☐☐☐ Subject Number ☐☐☐☐☐

Complete all of the investigator and subject number boxes provided. Use leading zeros, when necessary, to complete all expected boxes.

Example: Investigator #407 would be filled in as: 0 0 4 0 7

Subject Initials ☐☐☐

Record the first letter of the subject's first, middle and last name, in that sequence. If the subject has no middle name, enter a dash.

Example: A - C

Subject's Sex: ☐ Female ☐ Male

Subject's Weight: _____ kg

Subject's Date of Birth: ___ - ___ - ___ (DD - MMM - YYYY)

Subject's Ethnicity (check one only): ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not Available

Subject's Race (check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Not Available

Study Drug:	Study Drug Start Date: ___ - ___ - ___ (DD - MMM - YY) Study Drug Stop Date: ___ - ___ - ___ (DD - MMM - YY) OR ☐ Study Drug Continuing		
Dose:	Route:	Frequency:	Kit #:

First Day of Last Menstrual Period: ___ - ___ - ___ (DD - MMM - YY) Estimated Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)

Method of Contraception (check all that apply):
☐ Oral Contraceptive Pills ☐ Condoms ☐ Periodic Abstinence ☐ Progestin Injection or Implants ☐ Spermacide
☐ Diaphragm ☐ Intrauterine Device (IUD) ☐ Tubal Ligation ☐ Other, specify:_____

Reproductive History: ☐ Gravida _____ ☐ Para _____

Tests performed during pregnancy: ☐ None ☐ Unknown
☐ CVS Results: ☐ Normal ☐ Abnormal
☐ Amniocentesis Results: ☐ Normal ☐ Abnormal
☐ Ultrasound Results: ☐ Normal ☐ Abnormal

Pregnancy Outcome
Was pregnancy interrupted? ☐ Yes ☐ No
If yes, specify: ☐ Elective Termination ☐ Spontaneous Abortion ☐ Ectopic
Date of Termination: ___ - ___ - ___ (DD - MMM - YY)
If pregnancy was **not** terminated, specify pregnancy outcome (and provide infant outcome information)
☐ Vaginal Birth: ☐ Premature ☐ Term OR ☐ C-Section: ☐ Scheduled ☐ Emergency Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)
Infant outcome information: ☐ Normal ☐ Abnormal

Additional Case Details (if needed):

NOTE: For initial reporting email both the Pregnancy CTEP-AERS Report and this additional Pregnancy Information Form to the ADVL1515 COG Study Assigned Research Coordinator. For follow-up reporting, email only this Pregnancy Information Form to the ADVL1515 COG Study Assigned Research Coordinator (See Section 13.7).

APPENDIX IV: MEDICATIONS ASSOCIATED WITH PROLONGED QT_C

The use of the following medications should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references. For the most current list of medications, please refer to the following reference:
Woosley, RL and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date December 2nd, 2016, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

Medications that prolong QTc	
Amiodarone	Flecainide
Anagrelide	Fluconazole
Arsenic trioxide	Haloperidol
Azithromycin	Ibutilide
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Ciprofloxacin	Ondansetron
Citalopram	Pentamidine
Clarithromycin	Pimozide
Disopyramide	Procainamide
Dofetilide	Propofol
Domperidone	Quinidine
Droperidol	Sevoflurane
Dronedarone	Sotalol
Erythromycin	Thioridazine
Escitalopram	Vandetanib

Medications that MAY prolong QTc	
Aripiprazole	Lapatinib
Bortezomib	Lenvatinib
Bosutinib	Leuprolide
Ceritinib	Mirtazapine
Clomipramine	Nicardipine
Crizotinib	Nilotinib
Dabrafenib	Olanzapine
Dasatinib	Osimertinib
Degarelix	Pazopanib
Desipramine	Promethazine
Dolasetron	Risperidone
Eribulin mesylate	Sorafenib
Famotidine	Sunitinib
Foscarnet	Tacrolimus
Gemifloxacin	Vemurafenib
Granisetron	Venlafaxine
Isradipine	Vorinostat

APPENDIX V: PHARMACOKINETIC STUDY FORM

COG Pt ID # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg Body Surface Area: _____m^2

LY2606368 Dose Level: _____mg/m^2 LY2606368 Total Daily Dose: _____mg

Blood samples (2 – 3 ml) will be collected in EDTA tubes at the following time points: Day 1 (pre-infusion, 1 hr., 1.5 hrs., 2 hrs., 4 hrs., and 8 hrs. after beginning the infusion), Day 2 (24 hrs. [± 2 hrs.] after beginning the Day 1 infusion), Day 5 (96 hrs. [± 24 hrs.] after beginning the Day 1 infusion), Day 8 (during CBC evaluation), and Day 15 (pre-infusion and 1 hr. after beginning the Day 15 infusion) of Cycle 1.

Record the exact time the sample is drawn along with the exact time LY2606368 is given on Days 1 and 15.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to Day 1 LY2606368 infusion	___/___/___	|__|__| : |__|__|
LY2606368 Infusion on Day 1 Date:___/___/___ Start Time: |__|__| : |__|__| End Time: |__|__| : |__|__|				
2	**Day 1**	1 hr. after beginning Day 1 LY2606368 infusion	___/___/___	|__|__| : |__|__|
3	**Day 1**	1.5 hrs. after beginning Day 1 LY2606368 infusion	___/___/___	|__|__| : |__|__|
4	**Day 1**	2 hrs. after beginning Day 1 LY2606368 infusion	___/___/___	|__|__| : |__|__|
5	**Day 1**	4 hrs. after beginning Day 1 LY2606368 infusion	___/___/___	|__|__| : |__|__|
6	**Day 1**	8 hrs. after beginning Day 1 LY2606368 infusion	___/___/___	|__|__| : |__|__|
7	**Day 2**	24 hrs. (± 2 hrs.) after beginning Day 1 LY2606368 infusion	___/___/___	|__|__| : |__|__|
8	**Day 5**	96 hrs. (± 24 hrs.) after beginning Day 1 LY2606368 infusion	___/___/___	|__|__| : |__|__|
9	**Day 8**	During CBC evaluation	___/___/___	|__|__| : |__|__|
10	**Day 15**	Prior to Day 15 LY2606368 infusion		
LY2606368 Infusion on Day 15 Date:___/___/___ Start Time: |__|__| : |__|__| End Time: |__|__| : |__|__|				
11	**Day 15**	1 hr. after beginning Day 15 LY2606368 infusion	___/___/___	|__|__| : |__|__|

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.3.6. See Section 8.3 for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date:_____
(site personnel who is responsible for research sample collection)

APPENDIX VI: TISSUE STUDY FORM (REQUIRED TISSUE)

COG Pt ID # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Body Surface Area: _____m^2 LY2606368 Dose Level: _____mg/m^2
LY2606368 Total Daily Dose: _____mg

Tumor Sample Labeling:

Samples should be labeled with the following information:

Protocol number: **ADVL1515**
Institution: _____
Patient ID #: _____
Accession #: _____
Sample Date: _____
Site of Acquired Tissue: _____
Tissue obtained at (check one option below):
☐Diagnosis ☐Relapse

Shipment of Tumor Tissue:

Paraffin-embedded tumor specimens must be packaged appropriately and shipped at room temperature to Dr. Cynthia Wetmore (at the address below). If a tumor block is not available, please send as many scrolls from the tumor block and/or a minimum of 10 unstained slides may be shipped instead. Please indicate above the date of the sample, site of tissue acquisition and whether it was obtained at diagnosis or relapse. Shipments should be sent **Monday through Thursday only** for priority overnight delivery using the COG FedEx account (do not ship on Friday). One copy of this form should be uploaded into RAVE.

A second copy should be sent with the tissue sample to the lab address below.

Attn: Cynthia Wetmore, M.D., Ph.D.
Phoenix Children's Hospital
Center for Cancer and Blood Disorders
Room 25117
1919 E Thomas Road
Phoenix AZ 85016

Notes: _____

_____

_____

_____

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel who is responsible for research sample collection)

APPENDIX VII: PHARMACODYNAMIC STUDY FORM

COG Pt ID # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Body Surface Area: _____m^2 LY2606368 Dose Level: _____mg/m^2
LY2606368 Total Daily Dose: _____mg

Blood samples (5 ml) will be collected in consenting patients in CPT tubes during Cycle 1 at the following time points: Day 1 (pre-infusion) and Day 2 (24 hrs. after start of Day 1 infusion).

Record the exact time the sample is drawn along with the exact time LY2606368 is given on Day 1.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Collected (24-hr clock)
1	Cycle 1, Day 1	prior to LY2606368 infusion		|__|__| : |__|__|
LY2606368 Infusion on Day 1 Date:___/___/___ **Start Time:** |__|__| : |__|__| **End Time:** |__|__| : |__|__|				
2	Cycle 1, Day 2	24 hrs. after start of Day 1 LY2606368 infusion		|__|__| : |__|__|

One copy of this Pharmacodynamic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.5.6. See Section 8.5 for detailed guidelines for packaging and shipping PD samples.

Record any notes for Sample Storage Conditions below.

Notes: _____

_____

_____

_____

_____

_____

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel who is responsible for research sample collection)

APPENDIX VIII: ISOLATION OF PBMCS AND PLASMA FOR CORRELATIVE STUDIES

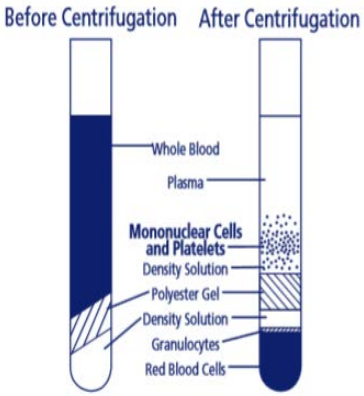
Isolation and Storage of Peripheral Blood Mononuclear Cells (PBMCs)

a) Purpose

To isolate Peripheral Blood Mononuclear Cells (PBMCs) for long term storage.

b) Equipment and Material Required

- Whole blood samples to be processed (freshly collected into CPT)
- Cell preparation tubes (CPT)
- Centrifuge (capable of centrifugation at 1,600 × rcf)
- Pipette and tips
- 0.5 ml and 2.0 ml cryo tubes (capable of being stored at -80˚C or -150˚C)
- Extra collection tubes (to counterbalance during centrifugation)
- 1 x PBS (room temperature)



c) Procedure

1. Gently invert CPT tubes 5 times before placing in the centrifuge
2. Counter balance extra collection tubes for centrifugation
3. Centrifuge the samples for 20 minutes at 1,600 × rcf at room temperature

   ***Ensure that tubes will not hit inside of centrifuge rotor once centrifugation begins
4. Remove tubes from centrifuge, ensuring that tubes are kept in the upright position so as not to disturb layers.
5. Aliquot plasma into labeled 2 ml aliquots, as appropriate (see SOP Processing Blood Samples Step 4 - 5)

   ***Be careful not to disrupt the cell layer while aspirating plasma (see image above)
6. Transfer small amount of remaining plasma and cells from CPT tubes into a 15 ml conical tube
7. Rinse CPT tubes using 5 ml of 1 × PBS (gently pipette up and down)

   ***Be careful not to disturb the gel matrix. Rinsing should remove most of the cells from the gel matrix. The wash may be reddish in color.
8. Transfer the rinse mixture into the same 15 ml conical tube (one tube per patient sample)
9. Discard the rinsed CPT tubes in the biohazard waste
10. Bring the total volume, in the 15 ml conical tube, to 15 ml using 1 × PBS

11. Mix the cells by gently inverting the tube 5 times
12. Centrifuge at 300 × rcf for 15 minutes at room temperature
13. Aspirate and discard the supernatant, being careful not to disturb the cell pellet
14. Add 200-500 µl of PBS to the cell pellet and pipette gently to resuspend pellet (use smallest volume of PBS to fully resuspend pellet)
15. Aliquot resuspended cells into 0.5 ml labeled cryo tubes and place in -80˚C freezer until shipment.

APPENDIX IX: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	≤ 1.5X
Grade 2:	> 1.5X- 3X
Grade 3:	> 3X-10X
Grade 4:	> 10X

ALT: For the purpose of this study, the ULN for ALT is 45 U/L regardless of baseline.

Grade 1:	≤ 135
Grade 2:	136- 225
Grade 3:	226- 900
Grade 4:	> 900

AST: For the purpose of this study, the ULN for AST is 50 U/L regardless of baseline.

Grade 1:	≤ 150
Grade 2:	151-250
Grade 3:	251-1000
Grade 4:	> 1000

GGT:

Grade 1:	≤ 2.5X
Grade 2:	> 2.5X- 5X
Grade 3:	> 5X-20X
Grade 4:	> 20X

APPENDIX X: CTEP AND CTSU REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

CTSU Registration Procedures

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

IRB Approval:
Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Requirements for ADVL1515 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.