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CHILDREN'S ONCOLOGY GROUP

ADVL1414

A PHASE 1 STUDY OF SELINEXOR (KPT-330, [redacted]), A SELECTIVE XPO1 INHIBITOR, IN RECURRENT AND REFRACTORY PEDIATRIC SOLID TUMORS, INCLUDING CNS TUMORS

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

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[redacted]

For PEP-CTN Operations and Data/Statistics Contacts see: http://members.childrensoncologygroup.org

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[redacted]

AGENT NSC# AND IND#'s
Selinexor (KPT-330, NSC#781780, [redacted])

SEE SECTION 8.3.5 AND APPX. IV-V FOR SPECIMEN SHIPPING ADDRESSES

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ABSTRACT

Recurrent pediatric brain and solid tumors, especially high-grade gliomas (HGG), have few effective treatments and are a major source of mortality in pediatric oncology. XPO1 (CRM1) is a nuclear export protein that selectively transports tumor suppressor (TSP) and growth regulatory (GRP) proteins out of the nucleus, effectively inhibiting their function. Selinexor (KPT-330), a novel small molecule, slowly reversible inhibitor of XPO1, is the first-in-class **S**elective **I**nhibitor of **N**uclear **E**xport (SINE). Selinexor causes the retention, accumulation, and activation of TSP/GRP in the nucleus, which in turn induce cell cycle arrest wherein neoplastic cells with genomic deoxyribonucleic acid (DNA) damage undergo apoptosis. Selinexor has demonstrated preclinical efficacy in multiple pediatric cancer models, including intracranial xenografts of HGG. In phase 1 trials in adults, selinexor has been generally well tolerated with common side effects of fatigue, nausea, vomiting, diarrhea, and dehydration, which can be effectively managed with supportive care. Selinexor has received accelerated FDA approval for the treatment of relapsed or refractory multiple myeloma in combination with dexamethasone in adult patients who have received at least 4 prior therapies and whose disease was refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. Selinexor has also demonstrated promising preliminary clinical activity in acute myeloid leukemia, glioblastoma multiforme (GBM), sarcoma, and other solid tumors. We will conduct a phase 1 trial of selinexor in children with recurrent brain and solid tumors using the Rolling Six design. The aims of the trial will be to establish the maximum tolerated pediatric dose of selinexor; to investigate the toxicities, pharmacokinetics, and pharmacodynamics of selinexor in children with these tumors; and to preliminarily explore efficacy in pediatric solid and CNS tumors, including medical and surgical expansion cohorts of HGG patients.

EXPERIMENTAL DESIGN SCHEMA

(Pre-Amendment #1):

Week	Day	Agent: Selinexor (KPT-330)
1	1, 3 (Dose 1,2)	X
2	8, 10 (Dose 3,4)	X
3	15, 17 (Dose 5,6)	X
4*	22, 24 (Dose 7,8)	X

* Evaluations will occur at the end of cycle 1, every other cycle x 2, then every 3 cycles

(Amendment #1):

Week	Day	Agent: Selinexor (KPT-330)
1	1, 3 (Doses 1,2)	X
2	8, 10 (Doses 3,4)	X
3	15, 17 (Doses 5,6)	X

4	Rest	

Amendment #4:

Week	Day	Agent: Selinexor (KPT-330)
1	1	X
2	8	X
3	15	X
4	22	X

With Amendment #4, patients will receive selinexor once weekly, on Days 1, 8, 15, and 22 of a 28-day cycle. Therapy will be discontinued if there is evidence of progressive disease or drug-related dose-limiting toxicity that requires removal from protocol therapy.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the recommended phase 2 dose (RP2D) or the maximum tolerated dose (MTD) of the tablet formulation of selinexor in children with recurrent/refractory solid and CNS tumors.

1.1.2 To describe the toxicities of selinexor in children with recurrent/refractory solid and CNS tumors.

1.1.3 To characterize the pharmacokinetics of the tablet formulation of selinexor in children with recurrent/refractory solid and CNS tumors.

1.2 Secondary Aims

1.2.1 To determine the antitumor effect of selinexor in a preliminary manner in children with recurrent/refractory solid and CNS tumors.

1.2.2 To determine the pharmacodynamic properties of selinexor in children and adolescents with refractory solid tumors in plasma proteins and whole blood RNA.

1.2.3 To explore the penetration, pharmacodynamic effects, and biologic effects of selinexor in tumor tissue of patients with recurrent/refractory HGG requiring resection.

1.2.4 To further assess the toxicity and antitumor effects of selinexor in children with recurrent/refractory HGG in expanded cohorts following dose-escalation by measuring rate of objective radiographic response (medical patients) and rate of progression-free survival (PFS) six months from the start of treatment (surgical patients).

2.0 BACKGROUND

2.1 Tumor suppressor function and selinexor

Over 10 major tumor suppressor pathways have evolved in order to prevent the development

and progression of carcinogenesis. The majority of the tumor suppressor (TSP) and growth regulatory (GRP) proteins mediating these pathways act in the cell nucleus. Accumulating data suggest that in order to maintain their malignant behavior, neoplastic cells must inactivate most or all of the known TSP and GRP pathways.[1] Active nuclear export of TSP/GRP is one very efficient and rapid means of overcoming normal cell cycle regulation and the genomic stability assessment mediated by these proteins.

Essentially all known TSP/GRP utilize a single non-redundant nuclear export protein complex to exit the nucleus. Exportin 1 (XPO1), also known as chromosomal region maintenance protein 1 (CRM1), is the primary component of this export complex, and is overexpressed in many types of cancer.[2] Approximately 200 different mammalian XPO1 cargo proteins are known,[3] including the vast majority of the TSP and GRP. XPO1 "recognizes" most of these cargo proteins for nuclear export through canonical Nuclear Export Sequences (NES) in the cargo protein. These NES are often buried within the cargo proteins and only unmasked when cells receive specific signals from their environments. XPO1 itself has a very specific cargo-binding groove that allows it to accommodate a diverse array of NES-bearing proteins.[3] In addition, XPO1 mediates the export of a small number of RNAs,[4] though most RNAs are exported by alternative mechanisms.[4]

Human cancers frequently overexpress XPO1 and/or show inappropriate cytoplasmic expression of TSP/GRPs, suggesting dysfunctional nuclear-cytoplasmic transport. XPO1 is upregulated in a range of solid tumors and hematologic malignancies, including high-grade glioma, and its overexpression is correlated with poor prognosis, suggesting that alterations in nuclear-cytoplasmic transport, and hence mislocalization of tumor suppressor proteins, cell cycle regulators, and/or pro-apoptotic proteins, could promote oncogenesis and resistance to chemotherapy. [5-9]

Selinexor is a **S**elective **I**nhibitor of **N**uclear **E**xport (SINE) that binds and inactivates XPO1 in a reversible manner, thereby forcing the nuclear retention of key TSP/GRP. Transient retention of TSP/GRP in the nucleus at high levels via XPO1 blockade activates cell cycle checkpoint and genomic surveying. This leads to the death of nearly all types of malignant cells, whereas normal cells undergo transient cell cycle arrest and recovery when the export block is released.

2.2 Rationale for the Current Study

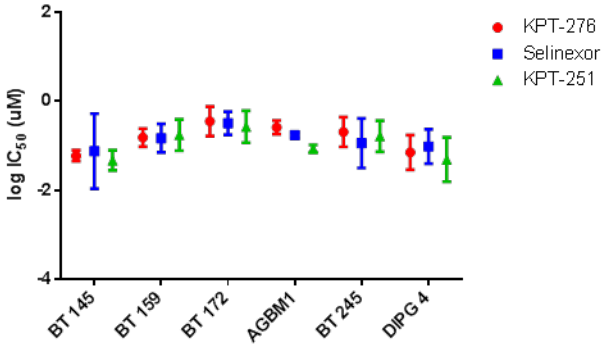
Survival following chemotherapy for pediatric malignancy remains one of the most stunning successes of modern medicine. Overall, nearly 80% of children with cancer treated in developed countries will be cured of their disease.[10] Nevertheless, despite significant intensification of therapy, there remains a subset of patients with aggressive non-hematologic malignancies, notably pediatric and adolescent sarcoma and brain tumors, for whom treatment gains have been relatively modest over the past two decades.[11] The situation is especially dire in pediatric high-grade gliomas (HGG). HGG are defined as World Health Organization grade III and IV tumors of glial origin. They occur in both adults and children. Preclinical studies of selinexor in pediatric brain and solid tumors, combined with promising safety and efficacy data seen so far in adults, make selinexor an excellent candidate for use in this early-phase clinical trial in children with recurrent/progressive brain and solid tumors, who have few treatment options.

2.3 Preclinical Studies

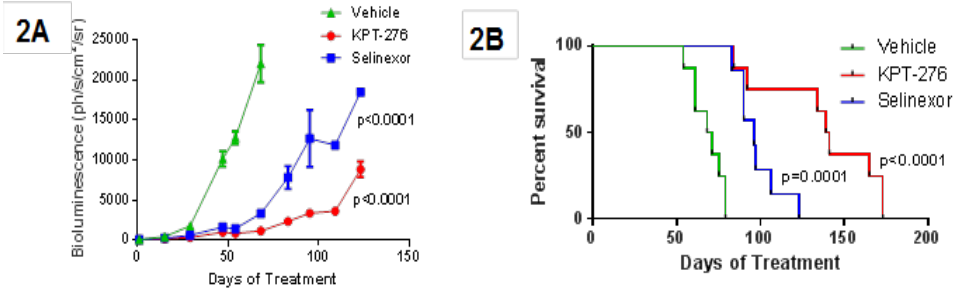
2.3.1 Antitumor Activity in Pediatric Malignancies

XPO1 is overexpressed in osteosarcoma when compared to normal tissue and is associated with higher grade and inferior progression-free and overall survival rates.[9] Similarly, in high-grade glioma (HGG), overexpression of XPO1 correlates with tumor grade and survival.[7] Investigators from Dana-Farber and Columbia University recently published data showing dose-response curves in multiple adult and pediatric primary human HGG lines to XPO1 inhibitors KPT-276, selinexor, and KPT-251.[12] Cells in neurosphere culture in triplicate in 96-well plates from each line were treated with a log-scale range of drug concentrations, from 0.1 nM to 100 uM, for a period of five days. Control cells were treated with DMSO alone. Survival was measured using the CellTiter Blue assay. IC_{50} values fell within a narrow, sub-micromolar range as seen in figure 1 (with 95% CI).

Figure 1:



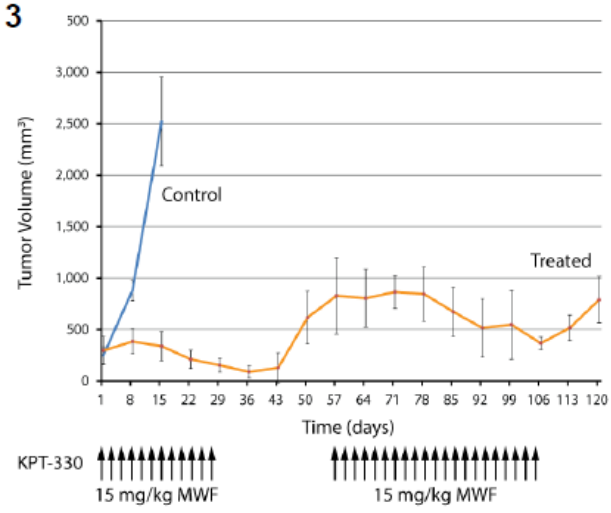
Three groups of 10 mice each were then injected intracranially with adult primary human glioma cells infected with a luciferase virus to allow serial imaging. When the bioluminescence level of the tumors was steadily increasing, treatment began with KPT-276, selinexor, or control vehicle. Both XPO1 inhibitors had a significant effect on the rate of tumor growth and survival. The main side effect in the mice was weight loss, which could be overcome with dosing adjustments.

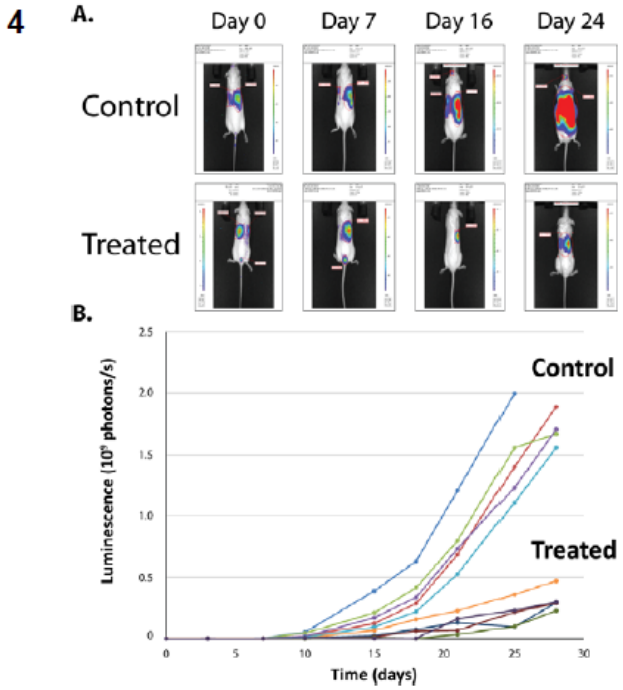


The Pediatric Preclinical Testing Program (PPTP) also recently tested selinexor against their panel of pediatric cell lines both *in vitro and in vivo* (Houghton PJ et al, AACR Annual Meeting 2013, Poster LB-354). The median relative IC_{50} (rIC_{50}) was 125 nM (range 13 nM to > 10 µM), with a trend for greater sensitivity for the Ewing sarcoma cell lines (median rIC_{50} = 57 nM) and lesser sensitivity for the neuroblastoma cell lines (median rIC_{50} = 235 nM). In subcutaneous murine models, selinexor was administered at 10 mg/kg orally on a 3-day/week schedule (M-W-F) for 4 weeks with a total treatment/observation period of 6 weeks.

selinexor showed tumor regression in 3 of 38 (4%) solid tumor xenografts, including a maintained complete response (MCR) in a Wilms (1 of 3), a CR in a slow growing ependymoma (1 of 2) and a CR in a medulloblastoma (1 of 2) xenograft. Tumor growth inhibition meeting criteria for intermediate or high activity was demonstrated in 11 of 32 (34%) of the solid tumor panel, most frequently for the Wilms (2 of 3) and Ewing sarcoma (4 of 5) models.[13]

Investigators at the Children's Hospital of Philadelphia (CHOP) have demonstrated that XPO1 mRNA expression is higher in neuroblastoma cell lines and *MYCN* amplified primary tumors when compared to low-risk tumors. They tested a panel of 17 neuroblastoma cell lines *in vitro* over a 5-log range of selinexor.[14] All cell lines tested were sensitive to selinexor with IC_{50} values ranging from 51-568 nM. While the *in vivo* models of the PPTP showed progressive disease in six neuroblastoma models with selinexor at 10 mg/kg MWF, the data from CHOP show objective responses at higher selinexor doses. Flank xenografts of the neuroblastoma cell line SH-SY5Y showed tumor size reduction after oral administration of selinexor at 15 mg/kg MWF. Perhaps more importantly, resistance was not observed. After allowing the tumors to grow following 28 days of drug withdrawal, re-exposure to the drug again showed growth suppression (Figure 3). Selinexor was also tested in a model of disseminated neuroblastoma created by tail vein injection of a luciferase-expressing SH-SY5Y line. Tumor growth was monitored by luciferase imaging which was correlated with serial necropsies (Figure 4A). Mice treated with selinexor (15 mg/kg MWF) showed suppression of tumor growth (Figure 4B) and prolonged survival. Liver metastases harvested at necropsy showed decreased Ki-67 and increased caspase-3 staining in treated tumors as compared to controls. Similar results were seen with the IMR5 and Be2c neuroblastoma cell lines. [14-16]





Selinexor, as well as other SINE compounds, have also been studied in preclinical leukemia models. The dosing regimen was every other day x 3 each week (QoDx3/wk); anti-tumor activity has also been shown with twice weekly dosing. Efficacy was demonstrated at doses of 15-60 mg/m^2 (5-20 mg/kg) in mouse models of T-cell acute lymphocytic leukemia (T-ALL) xenografts. Moreover, efficacy, including significant survival advantages, was demonstrated in acute myeloid leukemia (AML) [MV4-11 (FLT3-ITD)], chronic myeloid leukemia in blast crisis (CML-BC), and T-ALL leukemografts.[15,16]

2.3.2 Animal Toxicology

Sprague-Dawley rats and cynomolgus monkeys were chosen as the toxicology species for the selinexor nonclinical safety program. In both species, the primary effects of selinexor were dose-dependent reductions in food intake and body weight (or reductions in body weight gain), with minimal clinical symptoms (no or mild non-bloody diarrhea), associated primarily with gastrointestinal atrophy. Similar effects are observed in mice and dogs given selinexor and related SINE compounds. Increases in amylase and/or lipase, ALT (with less effects on AST), CK, and LDH were observed, but generally were not indicative of organ failure across species. Dose-dependent lymphocyte depletion in lymphoid organs was observed, with alterations in blood hematology parameters generally considered to be clinically insignificant. In summary, dose limiting toxicity (DLT)/mortality in both rats and monkeys is related primarily to marked weight loss at high repeated doses of selinexor with atrophy of the gastrointestinal (GI) tract and noncritical effects on other major organs.

In rats, DLT was related to subacute progressive weight loss and GI tract atrophy across all of the studies. Acute single PO gavage doses of selinexor at up to 3,000 mg/m^2 (500 mg/kg) showed no mortality at up to 24 hours post-dose. There were dose-dependent reductions in food and water intake and body weight, and non-bloody diarrhea was observed. Clinically significant changes in serum chemistry (LFTs, CK, LDH) were observed at the highest dose tested, with no clinically significant changes in hematological or coagulation parameters. Gross necropsy showed thinning of the gastrointestinal wall. Monkeys showed similar DLTs as observed in rats, namely dose-dependent weight loss associated with reduced food intake that were both rapidly reversible. Animals that had >7.5% body weight loss were given Ensure® and additional food supplements during the study. The body weights of the recovery group animals returned to approximately baseline levels by the end of the recovery period (two weeks) and substantial recovery had already occurred by 4-5 days after dosing.

No CNS-related adverse side effects and no microscopic changes in the brain were observed in the rat and monkey Good Laboratory Practice (GLP), 4-week toxicity studies. However, in monkeys at doses >72 mg/m^2, marked rapid weight loss was observed and associated with abnormal muscle movements and histopathological changes in the cerebellar granular neurons and inner cell nuclear layer of the eye. No CNS-related toxicities observed after a single dose of selinexor or repeated doses <72 mg/m^2 in the monkey. Doses of 300 mg/m^2 in rats were also associated with cerebellar granular neuron changes without any CNS behavioral changes (Irwin test). The dose that resulted in 10% mortality over the duration of the study (STD10) in rats was >30 mg/m^2, and the highest non-severely toxic dose (HNSTD) in monkeys was 18 mg/m^2.[16]

Selinexor has been studied at 10 µM in an *in vitro* selectivity assay including receptors, kinases, and cysteine proteases (including caspases and matrix metalloproteinases), with none of the targets significantly affected by selinexor except for Monoamine Oxidase B (MAO-B; binding IC_{50} of >5 µM and minimal functional activity). Given the minimal inhibition of human Ether-à-go-go Related Gene (hERG) tail current density (hERG IC50) for selinexor is 20.6 µM in the absence of serum, and given the high plasma protein binding, it is unlikely for selinexor to have any clinically significant impact on hERG or associated cardiac conduction in humans. In the pivotal, GLP, 4-week monkey study, ECGs were recorded on all animals during the pretest period, and on all animals assigned to the study during the final dosing cycle (1-2 hours post dose on Day 21) and during the last week of the recovery period on Day 39. There was no ECG evidence of a direct or indirect effect of selinexor on the morphology and intervals of the ECG at up to 36 mg/m^2 (3 mg/kg). Based on these results, QT prolongation or other cardiac effect does not appear to be a safety concern for selinexor.

Selinexor was not mutagenic in a bacterial reverse mutation (Ames) test.

No preclinical toxicity studies in juvenile animals have been performed. Please refer to the Investigator's brochure for full details of preclinical toxicology studies.

2.3.3 Preclinical Pharmacokinetic Studies

Preclinical PK parameters were assessed in three species: mouse (CD1), rat (Sprague-Dawley), and monkey (cynomolgus). Oral bioavailability (F%) of selinexor was remarkably consistent among the three species, with average values of 66.5%, 61.2%, and 67.5% in mice, rats, and monkeys, respectively. Protein binding of selinexor was high in all species (>90%). Overall, systemic exposure was generally dose-proportional in all studies that involved multiple dose levels. No accumulation was observed. The drug underwent minimal metabolism *in vitro* by liver microsomes as well as minimal metabolism by the human liver S9 fraction; the major product of metabolism is GSH conjugation, with the formation of inactive metabolites including N-acetylcysteinyl- and cysteinyl-derivatives. Selinexor showed no significant *in vitro* interactions with any of the cytochrome P450 (CYP450) enzymes (*i.e.*, IC_{50} >10 µM), except for one substrate of CYP3A4 (testosterone) which displayed an IC_{50} of 4.7 µM (the IC_{50} for midazolam, the other CYP3A4 substrate, was >10 µM). No induction of CYP450 activity was observed for CYP1A2 or CYP3A4.

Higher C_{max} and earlier T_{max} values were observed in monkeys that were fasted versus fed prior to dosing. Systemic exposure (AUC_{last}) was not affected by the feeding status in monkeys. Delivery of drug product was studied using gelatin capsules and suspension. When cynomolgus monkeys were given a suspension formulation by nasogastric tube, exposure increased by 40%, and C_{max} increased threefold versus capsule dosing. Assessment of brain penetration two hours after single oral dosing of selinexor revealed brain:plasma ratios averaging 0.72 in rats and 0.61 in cynomolgus monkeys. Using standard techniques and allometric scaling the predicted human clearance of selinexor is 227 ml/h/kg, or approximately half the clearance rate observed in monkeys. Thus, the predicted exposure in humans is not expected to significantly vary from that observed in monkeys. Anticancer activity is anticipated at doses of 15-45 mg/m^2. At these

doses, C_{max} is expected to be 0.9-2.8 μM. [17]

2.4 **Adult Studies**

In phase 1 clinical trials in adults with advanced solid or hematological malignancies (NCT01607905, NCT01607892, and NCT01896505). Selinexor was administered to over 240 patients. The dose limiting toxicities (DLTs) on the initial solid tumor trial were anorexia/nausea/dehydration and fatigue at 40 mg/m^2 (10 times per 4-week cycle; Days 1, 3, 5 of weeks 1 & 3 and Days 1 & 3 of weeks 2 & 4). The MTD and recommended phase 2 dose (RP2D) for 10 times per cycle dosing is 30 mg/m^2. Reduced intensity dosing at twice weekly (8 times per cycle, Days 1 & 3 of each week) has shown improved tolerability, with an approximately 50% reduction in the observed rate of adverse effects. One of 6 patients at a dose of 35 mg/m^2 on the twice weekly schedule experienced a DLT of Grade 3 nausea, vomiting and fatigue; this patient also experienced concomitant *C. difficile* infection. [18] Dose escalation cleared the 40 mg/m^2, 50 mg/m^2 and 65 mg/m^2 levels without DLT, but there were 2 DLTs at 85 mg/m^2: hyponatremia and reversible cerebellar syndrome. Based on these results, MTD and RP2D of selinexor twice weekly is determined to be 65 mg/m^2. [19]

The most common grade 1/2 AEs were nausea (78%), fatigue (70%) and anorexia (68%) vomiting (60%). Other toxicity included dysgeusia, diarrhea, dehydration, and weight loss. Aggressive supportive care, including prophylactic administration of appetite stimulants and anti-nausea agents, improves tolerability, [20] and symptoms abate with time. Idiopathic reductions in platelets (10-20% Grade ≥ 3) have been observed but without clinically significant bleeding; anemia and neutropenia have been minimal. Patients have reported blurred or diminished vision, but without objective findings on ophthalmological examination. Dehydration was determined to be responsible for at least some of the instances of blurred vision. There were 8 events of worsening for pre-existing cataracts, and 5 of these required operation. The attribution to selinexor is hard to determine, as phase 1 patients tend to be older and very heavily pre-treated with chemotherapy and dexamethasone. Because it is impossible to exclude selinexor as a contributing factor to worsening of cataracts, it is our recommendation that patients with pre-existing cataracts be excluded from the trial.

There has been evidence of clinical activity with disease stabilization ≥ 24 weeks in hormone- and chemotherapy-refractory prostate cancer, colorectal cancer, squamous head and neck cancer, and endometrial sarcoma, and partial responses seen in a Kras mutant colorectal cancer, a BRAF WT melanoma, and an ovarian cancer. [21,19]

The ongoing hematologic malignancies phase 1 study includes patients with relapsed and refractory hematologic malignancies who enter the study with documented progressive disease. No DLTs were observed in the initial five cohorts at doses ranging from 16.8 to 55 mg/m^2 on the 10 dose per 4-week cycle schedule. On each of the 16.8 mg/m^2 and 23 mg/m^2 dose levels, 1 of 6 patients had non-dose-limiting Grade 3/4 thrombocytopenia. The most common AEs were similar to those observed in patients with advanced metastatic solid tumors and were mainly gastrointestinal (GI) in nature. Escalation proceeded with the twice weekly schedule at dose levels 35 mg/m^2, 45 mg/m^2 and 60 mg/m^2 levels without DLT. [22] Clear evidence of anti-tumor activity, including remission, in these heavily pretreated hematologic malignancy patients has been demonstrated in diseases including AML and NHL, with higher doses noted to be associated with greater reductions in AML blast count.[22-24] Prolonged administration of over four months has been found to be feasible, and no drug-associated deaths have occurred.[25]

(Amendment 4) On July 3, 2019, the FDA granted accelerated approval to selinexor in combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies and whose disease was refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. Approval was based on a subgroup analysis of 83 heavily pretreated patients enrolled on the STORM trial (KCP-330-012; NCT02336815) and treated with 80 mg selinexor (45 mg/m^2) in combination with dexamethasone on Days 1 and 3 of each week. Overall response rate was 25.3% (95% CI: 16.4, 36) with a median response duration of 3.8 months (95% CI: 2.3, not estimable). Adverse events reported in at least 20% of patients include thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.[26]

Several Phase 2 studies in solid and CNS tumors have recently opened or are in the late planning stages. In the phase 2, two-tier KING study (NCT01986348) evaluating the efficacy and safety of single-agent selinexor in patients with recurrent GBM after failure of radiation therapy and temozolomide, designed to start at 50 mg/m^2, nearly half of patients enrolled needed to de-escalate to 35 mg/m^2 during the first 8-dose cycle due to anorexia, nausea, dehydration and fatigue. The study was subsequently amended to begin at 35 mg/m^2 (60 mg flat dosing) twice weekly and to study 45 mg/m^2 (80 mg flat dosing) given once weekly. Both amended dosing schedules showed improved tolerability and similar efficacy. Investigators have reported results showing a 30% 6 cycle PFS rate and a 10% overall response rate at the 45 mg/m^2 weekly dosing.[27] No Grade 3 or 4 non-hematologic adverse events were reported on this arm; out of 30 subjects, Grade 3 neutropenia developed in 3 patients, and Grade 3 leukopenia, Grade 3 lymphopenia, and Grade 4 lymphopenia developed in 1 patient each.

2.4.1 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Detailed pharmacokinetic (PK) and pharmacodynamic (PD) analyses suggest a fairly proportional increase in C_{max} and AUC with increasing dose, with no accumulation and without affecting half-life or clearance. At 30 mg/m^2, $AUC_{0\text{-last}}$. (4375 ng*h/mL) was comparable to the anti-tumor exposure observed in mice and dogs. T_{max} (~3 h) and $T_{1/2}$ (6-7 h) were consistent across doses. Selinexor undergoes moderately rapid oral absorption, with median time to maximal plasma levels (T_{max}) of 1-8 hours. The volume of distribution is 1.5-2.5 L/kg, indicating good distribution to tissues beyond the central (vascular) compartment. The primary metabolic route is glucuronidation and hydroxylation of the parent drug. In addition, GSH conjugates with selinexor to form inactive metabolites including *N*-acetylcysteinyl- and cysteinyl-derivatives. Selinexor is not metabolized by CYP450.

Significant increase (2-20x) in XPO1 messenger ribonucleic acid (mRNA) levels in circulating leukocytes was observed at all doses, with higher doses demonstrating higher levels of XPO1 mRNA induction. Analysis of tumor biopsies confirmed nuclear localization of TSPs (e.g., p53, FOXO3A, IκB) and apoptosis of cancer cells following selinexor administration.[28]

As part of KCP-330-002 (the adult Solid Tumor phase 1), one patient (043-013) with mandibular cancer received selinexor through a feeding tube by opening capsules and adding the powder to water. This patient exhibited rapid selinexor

absorption, with an $AUC_{0\text{-}inf}$ of 4,520 ng*h/mL and C_{max} of 1,150 ng/mL. While exposure for patient 043-013 was similar to the mean exposure for the other 16 patients in the trial treated at 30 mg/m^2 with oral capsules, C_{max} was 3-fold higher than the corresponding mean. The rapid absorption and subsequent elevated C_{max} is likely related to the dose formulation, consistent with the preclinical finding in cynomolgus monkeys for the suspension formulation. Of note, there were no clinically significant AEs associated with this high C_{max}.

Data from KCP-330-003, a food effect study in patients with sarcomas (NCT01896505) has shown a 15% increased exposure to selinexor when patients take the medication with food, regardless of fat content, versus the fasting state.[20]

Several correlative biological studies have been initiated as part of the phase 1 trial, including study of XPO1 levels in peripheral white blood cells pre- and post-treatment. In addition, the KING trial includes a surgical arm allowing study of resected tumors after up to three doses of selinexor. This has included administration of the medication on the morning of surgery with a sip of water, up to two hours before induction of anesthesia. Patients have then been allowed to resume oral selinexor after recovery (1 to 5 weeks after surgery). There have been no adverse effects associated with this pre and post-operative administration of selinexor, including on wound healing (personal communication, Andrew Lassman). Studies on this tissue included measurement of intra-tumoral drug levels, as well as other assays examining pharmacodynamic effect of selinexor on tumor cells, including induction of apoptosis, and XPO1 mRNA and protein levels. Preliminary data from 7 patients showed that selinexor reached therapeutic concentrations of ~50-300 nM within brain tumor tissues, with a median plasma concentration of 122 nM in adult GBM after ~2 hours.[29]

2.5 Pediatric Studies

2.5.1 Prior Experience in Children (Updated with amendment 4):

In a pediatric Phase 1 trial of selinexor in children with recurrent/progressive leukemia run through the Dana-Farber Leukemia Consortium (DFCI), the recommended Phase 2 dose was determined to be 40 mg/m^2 twice weekly, 8 doses in a 28 day cycle.[30] Two DLTs were encountered: pancreatitis (30 mg/m^2) and cognitive disturbance (56 mg/m^2). Single agent activity was noted with an ORR of 12.5% [1 CRp (AML), 1 PR (ALL)] and 2 of 4 patients with ALL experienced Grade 4 tumor lysis syndrome.[30] In addition, as part of a St. Jude Hospital investigator sponsored trial evaluating selinexor (Days 1, 3, 8, 10, 22, and 24) with fludarabine and cytarabine (Days 15 through 19) for treatment of refractory or relapsed leukemia or myelodysplastic syndrome, the MTD of selinexor was 55 mg/m^2.[31] The dose-limiting toxicity at 70 mg/m^2 was reversible cerebellar toxicity, but at and above 40 mg/m^2, all patients treated demonstrated evidence of XPO1 target inhibition.[31]

2.5.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

The below table depicts pharmacokinetic results obtained from four pediatric patients dosed at 30 mg/m^2 twice weekly with selinexor. The data shows that pharmacokinetic parameters observed in pediatric patients (n=4) at 30 mg/m^2 are comparable to those observed in adult patients administered with the same selinexor dose.

	Cmax (ng/mL)	AUC_{0-8} (ng*h/mL)	AUC_{inf} (ng*h/mL)	Tmax (h)	T ½ (h)	Vd/F (mL)
Pediatric Patients						
Day 1	569	1893	4180	2.75	6.55	1866
Day 22[a]	425	1854	*NC*	2.67	*NC*	*NC*
Adult Patients						
Day 1	443	1959	3040	2.0	5.2	2078
Day 17	378	1849	*NC*	2.0	*NC*	*NC*

NC = not calculable
[a] One patient collected on Day 15

(Amendment 4) The updated pharmacokinetic data from the DFCI trial continue to demonstrate that the pharmacokinetics of selinexor in children are dose proportional and achieve exposures similar or slightly higher than that of adults. (Place et al ASH 2018).

2.6 Overview of Proposed Pediatric Study

We will conduct a phase 1 trial of selinexor in children with recurrent or refractory solid tumors, including CNS tumors using the Rolling Six design. The aims of the trial will be to establish the maximum tolerated pediatric doses of tablet formulation; to investigate the toxicities, pharmacokinetics, and pharmacodynamics of selinexor in children with cancer; and to preliminarily explore efficacy in pediatric solid and CNS tumors, including medical and surgical expansion cohorts of HGG patients.

After the recommended Phase 2 dose has been determined on the dose-escalation portion Part A, Parts B and C will open concurrently. During the initial cohort, patients received selinexor twice weekly (once on each day) on a days 1,3 schedule (Mon/Wed,Tue/Thurs, or Wed/Fri). One cycle was 28 days or 8 doses. Due to unanticipated hematological toxicity the schedule was revised (Amendment #1 April 2016) and subsequent patients received selinexor twice weekly (once on each day) on a days 1,3 schedule (Mon/Wed,Tue/Thurs, or Wed/Fri) during weeks 1-3, followed by a 7 day break. One cycle was 28 days or 6 doses. With Amendment #4, given evidence from adult trials showing equivalent efficacy of once and twice weekly dosing with increased tolerability when given once weekly, the once weekly dosing schedule will be tested. Each 28 day cycle will consist of selinexor given once a week for 4 doses.

Toxicity will be assessed using CTCAE v5.0. Imaging for disease evaluation during the dose escalation phase will occur at the end of Cycle 1, every other cycle x 2, and every 3 cycles thereafter. Disease response will be assessed according to RECIST v1.1 criteria for solid tumors and 2-dimensional measurement for CNS tumors.

2.7 Rationale for Change in Dosing Schedule (Amendment #1)

Upon initiation of ADVL1414 Part A, 6 patients were enrolled at Dose Level 1, 35 mg/m2 of selinexor by mouth twice weekly on a days 1 and 3 schedule for 8 doses within a 28-day course. Four patients completed course 1, were fully evaluable for toxicity for the purposes of dose escalation, and did not experience a DLT. Two patients were inevaluable for DLT during cycle 1: one for a protocol deviation regarding the use of cyproheptadine, which has been addressed in this amendment, and one for having received a platelet

transfusion when platelets were at a grade 2 (53K), wherein grade 3 thrombocytopenia (<50K) might have constituted a DLT. In addition, one patient who did not experience a DLT during cycle 1, developed a grade 4 neutropenia during cycle 2 (a protocol defined DLT), which recurred after dose reduction, and subsequently required removal from protocol therapy despite disease stabilization. This observed hematologic toxicity was beyond that which was anticipated based on the data from previous adult trials.

Selinexor is known to block megakaryocyte maturation. Neutropenia is rare. According to the Investigator's Brochure version 9.0, dated 13 August 2019, the incidence of grade 3/4 thrombocytopenia in patients with solid tumors was 12% and the incidence of grade 4 neutropenia was 0.3% (34.7% and 6.4% respectively, when including patients with hematologic malignancy). In our recent discussions, the drug company, Karyopharm, provided new data from several adult trials in which it was noted that selinexor induced thrombocytopenia. The platelet nadir occurred after one cycle. The magnitude of thrombocytopenia was independent of dose occurring at selinexor doses of 30-150 mg when given 2x wkly, for 7-8 doses/28 cycle. The percent decrease in platelet count was relatively constant (~50%) regardless of baseline platelet count. In our discussions with Karyopharm, dose reductions for hematological toxicity in adult receiving selinexor were not standardized. However, in review of data we concluded that interruption of selinexor therapy, and in cases of prolonged recovery (>3 weeks), decrease in dose frequency represent the optimal management for grade 3/4 thrombocytopenia. The mechanism of neutropenia is not currently known, less data is available but data indicates that neutropenia may be dose dependent and is responsive to granulocyte colony stimulating factor. Data on cumulative myelosuppression is not available.

Selinexor has a unique mechanism of action that allows this scheduling strategy. It acts by slowly reversibly inhibiting nuclear export of tumor suppressor proteins, which causes cancer cells to undergo a genomic fidelity review with each dose, leading to apoptosis. In the past, irreversible inhibition of the nuclear exporter XPO1 has been found to be highly toxic to normal cells, leading to the current requirement for intermittent dosing. The half-life of selinexor is approximately six hours.

2.8 Rationale for Change in Dosing Schedule (Amendment #4)

Over 2,601 patients have received selinexor to date through numerous clinical trials for a variety of malignancies, both as a single agent and in combination.[17] Despite the MTD determination of 65 mg/m^2/dose in adult single agent Phase 1 studies on the twice weekly (8 dose/ cycle) schedule, most studies are now using reduced doses of 35-45 mg/m^2/dose due to analysis of safety and pharmacokinetic data showing acceptable efficacy and improved long-term tolerability. The most recent FDA approval for multiple myeloma uses selinexor in combination with dexamethasone at the equivalent of 45 mg/m^2/dose (80mg flat dosing). Furthermore, it is clear from multiple adult trials of selinexor that weekly dosing, even at higher individual doses, reduces myelosuppression and neurotoxicity compared to twice weekly dosing. Positive results have been presented in patients with sarcoma,[32] acute myeloid leukemia, diffuse large B cell lymphoma, and others.

In the Phase 2 trial of selinexor in recurrent glioblastoma (the KING trial), investigators have reported results showing a 30% 6 cycle PFS rate and a 10% overall response rate using the flat 80 mg weekly schedule (equivalent to 45 mg/m^2).[27] No Grade 3 or 4 non-hematologic adverse events were reported using this dose and schedule which was the regimen that was most effective and best tolerated; out of 30 subjects, there were no non-hematologic Grade 3/4 events, Grade 3 neutropenia developed in 3 patients, and Grade 3 leukopenia, Grade 3 lymphopenia, and Grade 4 lymphopenia developed in 1 patient each.

Investigators also demonstrated average intratumoral drug levels of 122 nM, on par with the *in vitro* IC_{50} described in the preclinical studies in adult and pediatric HGG.[6]

Comparative pharmacokinetic (PK) analysis between ADVL1414 and multiple adult studies suggest C_{max} and AUC values at 20 mg/m^2 were similar to those seen at 35 mg/m^2 dosing in adults, and values at 35 mg/m^2 compared favorably to those seen at doses up to 60 mg/m^2 in adults. 35 mg/m^2 dosing in children would therefore appear to produce at least equivalent PK values to the 80 mg flat dosing that produced the best responses in the KING trial, even when given weekly. A dose of 20 mg/m^2, on the other hand, is unlikely to produce adequate exposure for CNS tumor response, based on available clinical and preclinical data. Since progress in the trial to this point has demonstrated 20 mg/m^2 twice weekly (40 mg/m^2 cumulative per week) to be tolerable, we will use 45 mg/m^2 (a 12.5% increase in dose intensity) as our starting dose on the once weekly schedule which is anticipated to be less toxic than twice weekly dosing. We will have one dose escalation to 55 mg/m^2 and one available de-escalation to 35 mg/m^2, the lowest dose considered likely to produce adequate CNS exposure to be efficacious based on available evidence. We hypothesize that tolerability will be improved, that the RP2D for weekly dosing will be higher than the current RP2D for twice weekly dosing, and that C_{max} and AUC values equivalent or higher will be achieved and compare favorably to the dosing levels in adults at which responses have been observed.

Table A:

		Dose (mg/m^2)	Tmax (hr)	Cmax (ng/ml)	$t_{1/2}$ (hrs)	AUC (hr*ng/ml)	Cl/F (L/hr/m^2)
ADVL1414	Solid Tumors; Tablet with food Schedule- Days 1, 3, 8, 10, 15, 17, [22, 24]; PK- T= 0, 0.5, 1, 3, 4, 6, 8, 24 h	35, (n=19)	2 (0.5-6)	535 ± 174	7.9 ± 4.1	5156 ± 1227	7.12 ± 1.34
		20 (n=12)	4 (1-6)	324 ± 116	7.2 ± 1.2	3092 ± 842	6.98 ± 1.55
Alexander et al, 2016	Pediatric Acute Leukemia, No acetaminophen; Schedule- Days 1, 3, 8, 10, 22, and 24. PK- T=0, 0.5, 1, 2, 4, 8, 24, 48 h	30 + fludarabine (n=4)	3 ± 1.5	537 ± 281	6 ± 1	AUC_{0-48h} = 4,351 ± 513	
Abdul Razak et al, 2016	Adult Solid Tumors Schedules- Multiple; PK- T= 0, 0.5, 1, 2, 4, 8, 24, 48 h	20 (n=5)	4 ± 3	237 ± 105	6 ± 1	AUC_{0-48h} = 2,614 ± 603	
		35 (n=10)	4 ± 2	358 ± 82	7 ± 4	AUC_{0-48h} = 3,901 ± 932	
Gounder et al, 2016	Advanced Refractory Bone or Soft Tissue Sarcoma, Schedule- D1, D3 q Wx3 → 1 week off; Food Effect Study; PK- T= 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 24 h	30 (n=12); 1st gen tab, low-fat meal	3.5 ± 1.7	448 ± 88	5.5 ± 1.0	3,647 ± 648	
		60 mg (n=12); fed, oral suspension	1.8 ± 2.5	482 ± 218	6.7 ± 1.6	4,048 ± 771	
Lassman et al, 2017 WFNOS 5th Quadrennial Meeting Zurich, Switzerland.	KPT-330 (selinexor) IN patients with recurrent Gliomas (KING)	50, BIW pre- and post-surgery		C_{1hr} = 836 nM (370 ng/ml) C_{2hr} = 967 nM (429 ng/ml)			

Values for T_{max} are median (range); Values for all other results are mean (SD)

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. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

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

Local IRB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit 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 using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

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

3.3 Patient Registration in the COG Registry

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

3.4 Reservation and Contact Requirements

Once a slot-reservation confirmation is obtained after making a reservation in OPEN, the Study Chair or Vice Chair should be notified and site staff may then proceed to enroll patients to this study. (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. Note: See Section 4.1.3 for exceptions.

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 ADVL1414 COG Study Assigned 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 recheck 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).

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 BSA: Patients must have a BSA ≥ 0.84 m^2.

4.1.3 Diagnosis:

4.1.3.1 Part A: Patients with recurrent or refractory solid tumors, including lymphoma and 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 patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG.

4.1.3.2 Part B: Patients with recurrent or refractory high grade glioma (WHO Grade III/IV) including disseminated tumors (excluding DIPG), not requiring surgical resection. Patients must have had histologic verification of malignancy at original diagnosis or relapse.

4.1.3.3 Part C: Patients with recurrent or refractory high grade glioma (WHO Grade III/IV) and requiring surgical resection (excluding DIPG and disseminated tumors), who in the opinion of treating physicians, are medically stable to receive 2 doses of selinexor (8-10 days of treatment) before undergoing surgery without compromising the success of the procedure. Note that if, in the opinion of treating physicians, current symptoms necessitate surgery before 2 doses will be able to be received, surgery should not be delayed to administer selinexor, and the patient would be ineligible for protocol therapy.

4.1.4 Disease Status:

Part A: Patients must have either measurable or evaluable disease (see Sections 12.2 and 12.3 for definitions).

Parts B & C: Patients must have measurable disease on imaging.

4.1.5 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.

4.1.6 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.

4.1.7 Prior Therapy

4.1.7.1 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 numerical eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

a. Myelosuppressive chemotherapy: At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).
b. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) 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.
c. Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. 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.
d. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.
e. 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
f. 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.
g. XRT: At least 14 days after local palliative XRT (small port); At least 150 days must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; At least 42 days must have elapsed if other substantial BM radiation.
h. Stem Cell Infusion without TBI: No evidence of active graft vs. host disease and at least 56 days must have elapsed after transplant or stem cell infusion.
i. Patients must not have received prior exposure to selinexor.

4.1.8 Organ Function Requirements

4.1.8.1 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 ≥ 100,000/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 RBC transfusions)

b. Patients with known bone marrow metastatic disease will be eligible for study if they meet the blood counts in 4.1.8.1.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 on Part A must be evaluable for hematologic toxicity.

4.1.8.2 Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70 ml/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.

4.1.8.3 Adequate Liver Function Defined as:

- Total Bilirubin ≤ 1.5 × upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 3 × ULN = 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

4.1.8.4 Adequate Pancreatic Function Defined as:

- Serum amylase ≤ 1.5 x ULN
- Serum lipase ≤ 1.5 x ULN

4.1.9 Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.

4.1.10 Patients must be able to swallow tablets whole.

4.1.11 Part C: Archived paraffin-embedded tissue (20 unstained slides or a tumor block) from a prior resection must be available as a control for correlative studies. If tissue blocks or slides are unavailable, the study chair must be notified prior to enrollment.

4.1.12 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.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study, since there is yet no available information regarding human fetal or teratogenic toxicities. Based on its mechanism of action and findings in animals, selinexor may cause fetal harm when administered to a pregnant woman. Pregnancy tests must be obtained in girls who are post-menarchal. Males with female partners of reproductive potential or females of reproductive potential may not participate unless they have agreed to use two effective methods of birth control- including a medically accepted barrier method of contraceptive method (e.g., male or female condom) for the entire period in which they are receiving protocol therapy and for at least 1 week following their last dose of study drug. Abstinence is an acceptable method of birth control.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (See Section 4.1.7.1.f).

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.

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

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

4.2.5 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.

4.2.6 Patients with BMI < 3rd percentile for age, as defined by WHO criteria for patients 1-2 years of age and CDC criteria for patients > 2 years of age, are not eligible. (See Appendix IX)

4.2.7 Patients with grade 3 ataxia or grade >1 extrapyramidal movement disorder are not eligible.

4.2.8 Patients with known macular degeneration, uncontrolled glaucoma, or cataracts are not eligible.

5.0 TREATMENT PROGRAM

5.1 Treatment Overview

(Pre-Amendment #1):

Week	Day	Agent: Selinexor
1	1, 3 (Doses 1,2)	X
2	8, 10 (Doses 3,4)	X
3	15, 17 (Doses 5,6)	X
4	22, 24 (Doses 7,8)	X

Patients will receive selinexor twice weekly on a days 1,3 schedule (Mon/Wed, Tues/Thurs, or Wed/Fri). A cycle of therapy will be 28 days or 8 doses. The drug will be administered in tablet form with food. Patients may continue for a maximum of 24 cycles. Refer to section 7.3 for recommended supportive care guidelines.

(Amendment #1):

Week	Day	Agent: Selinexor
1	1, 3 (Doses 1,2)	X
2	8, 10 (Doses 3,4)	X
3	15, 17 (Doses 5,6)	X
4	Rest	

With Amendment #1, patients will receive selinexor twice weekly on a days 1,3 schedule (Mon/Wed, Tues/Thurs, or Wed/Fri) on Weeks 1-3, followed by a one-week rest period. A cycle of therapy will be 28 days or 6 doses. The drug will be administered in tablet form with food. Patients may continue for a maximum of 24 cycles. Refer to section 7.3 for recommended supportive care guidelines.

Amendment #4:

Week	Day	Agent: Selinexor
1	1	X
2	8	X
3	15	X
4	22	X

With Amendment #4, patients will receive selinexor once weekly, on Days 1, 8, 15, and 22 of a 28-day cycle. The drug will be administered in tablet form with food. Patients may continue for a maximum of 24 cycles. Refer to Section 7.3 for recommended supportive care guidelines.

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 (See Appendix VI). If a dose is vomited within 30 minutes of administration and there is visible evidence of the tablet, the dose should be repeated. If the tablet is not visible, or the dose is vomited later than 30 minutes after administration, the dose should not be repeated. The patient/caregiver should make a note of the vomited dose and whether there is visible evidence of the tablet on the pill diary and proceed with the next dose at the next scheduled time of administration.

Selinexor is supplied by Karyopharm Therapeutics. **Do not use commercial supply.**

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: Part A

The starting dose will be 35 mg/m^2 (dose level 1), with dose levels for subsequent groups of patients as follows.

(Pre-Amendment #4): Twice weekly dosing

Table for Dose Levels 1-3.

Dose Level**	Selinexor Dose (mg/m^2)
-1	20
1*	**35**
2	45
3	60^

* Starting Dose Level
^ Further dose escalation will be considered after evaluation of the pharmacokinetics and toxicity profile

Amendment #4: Once weekly dosing
Table for Dose Levels 1 & 2:

Dose Level**	Selinexor Dose (mg/m^2)
-1	35
1*	**45**
2	55

* Starting Dose Level

Amendment #4: With amendment #4, the starting dose will be 45 mg/m^2. Prophylactic treatment of nausea and emesis (such as 5-HT3 antagonists +/- another agent [e.g., dexamethasone, NK1 receptor antagonist, etc]) is strongly recommended during Cycles 1 and 2 (see Section 7.3). In adult patients, double antiemetic coverage (5HT3 antagonist + another agent) is preferred. If DLT of vomiting or dehydration is experienced in ≥ 2/6 evaluable patients at a dose level outlined in the dose level tables above, the dose level will be repeated with required maximal antiemetic therapy (5-HT3 antagonist PLUS antiemetic agent(s)) prior to each dose during Cycles 1 and 2. Once the requirement for prophylaxis during Cycles 1 and 2 has been made, this will be carried forward for all subsequent patients entered at the same or higher dose level. Dose levels which require antiemetic prophylaxis will be denoted with the suffix letter "A" (e.g. Dose Levels -1A, 1A, or 2A).

Selinexor is supplied by Karyopharm Therapeutics. **Do not use commercial supply.**

5.3.2 Part B: Non-Surgical HGG Expansion Cohort

Patients with HGG not requiring resection will be treated at the recommended phase 2 dose (RP2D) determined from the phase 1 component (Part A) of this trial.

5.3.3 Part C: Surgical HGG Expansion Cohort

Patients with HGG requiring resection (Part C) will be treated at the recommended phase 2 dose (RP2D) determined from the phase 1 component (Part A) of this trial for 2 doses prior to undergoing scheduled resection of their tumors (*i.e.* Surgical resection should occur after dose on Day 8 but before dose on Day 15 of Cycle 1). After recovery from surgery with wound healed (minimum 3 weeks) and meeting criteria in Section 5.2, patients can resume selinexor at the same dose and schedule and continue therapy to complete Cycle 1 and continue with Cycle 2. Patients who fail to recover from surgery within 6 weeks will be removed from protocol therapy.

5.3.4 Intra-Patient Escalation

Intra-patient dose escalation is not allowed.

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/protocolDevelopment/electronic_applications/ctc.htm). 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 selinexor. 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

- Any Grade 4 non-hematological toxicity
- Any Grade 3 non-hematological toxicity with the specific exception of:
  - Grade 3 nausea, vomiting, or dehydration that resolves to Grade ≤ 2 within 3 days. For the purposes of this pediatric study, tube feeding should not be considered a Grade 3 DLT. See Section 7.3 for supportive care guidelines.
  - Grade 3 anorexia. See Section 7.3 for supportive care guidelines
  - Grade 3 weight changes. See Section 7.3 for supportive care guidelines.
  - Grade 3 diarrhea that resolves to Grade ≤ 2 within 7 days
  - Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days. See Appendix VIII for values that represent thresholds between CTCAE grades.
  - Grade 3 bilirubin that returns to meet eligibility criteria within 7 days. See Appendix VIII for values that represent thresholds between CTCAE grades.
  - Grade 3 infection of < 5 days duration
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, hypomagnesemia, or asymptomatic hyponatremia responsive to oral supplementation
- Fever greater than 40°C of ≥ 5 days duration will be considered dose-limiting
- Any ≥ grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires two doses omitted in a cycle.
- Any toxicity that requires treatment interruption as outlined in Sections 6.3-6.7 and does not resolve within the specified time frame will be considered dose-limiting.

5.5.2 Hematological dose limiting toxicity

In patients evaluable for hematological toxicity (See Section 4.1.8.1),

- Grade 4 thrombocytopenia (platelet count < 25,000/mm^3), Grade 4 anemia, or Grade 4 neutropenia, not due to malignant infiltration
- Grade 3 thrombocytopenia that persists for ≥ 7 days
- Grade 3 thrombocytopenia requiring a platelet transfusion on 2 separate days, within a 7 day period
- Grade 3 thrombocytopenia with clinically significant bleeding, petechiae or purpura
- Myelosuppression that causes a delay of >14 days between treatment cycles.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

6.1 Dose Modifications for Hematological Toxicity

6.1.1 If a patient experiences Grade 4 neutropenia, selinexor should be held. Institute short acting granulocyte colony stimulating factor (filgrastim or biosimilar) as per institutional guidelines. Counts should be checked every 2 – 3 days until recovery to Grade ≤ 2 or baseline and without fever (if febrile) and the patient is clinically stable. If this is a first occurrence, and myelosuppression has lasted ≤ 7 days, the patient may continue at the same dose. If lasting for > 7 days or this is a second occurrence resulting in a missed dose, reduce selinexor by 1 dose level. If the occurrence falls on Day 1 of a cycle, delay start of the cycle, institute short acting granulocyte colony stimulating factor as per institutional guidelines, and check neutrophils every 2 – 3 days until recovery to Grade < 2 and eligibility is met to begin the next cycle. If the toxicity recurs, the patient may resume treatment at the currently assigned dose with a change in the schedule to weekly dosing for 3 weeks followed by a 1 week rest.

6.1.2 If a patient experiences either Grade 4 or dose-limiting Grade 3 thrombocytopenia as defined in Section 5.5.2, selinexor should be held. Counts should be checked every 2 – 3 days until any bleeding has stopped, patient is clinically stable, and the platelets have recovered to meet eligibility to begin the next cycle. When resuming selinexor, reduce by 1 dose level. If the occurrence falls on Day 1 of a cycle, delay start of the cycle and check platelet counts every 2 – 3 days until the platelets have recovered to meet eligibility to begin the next cycle. When resuming selinexor, reduce by 1 dose level. If the toxicity recurs, the patient may resume treatment at the currently assigned dose with a change in the schedule to weekly dosing for 3 weeks followed by a 1-week rest.

6.1.3 If a patient experiences myelosuppression not otherwise specified above that causes a delay of >14 days between treatment cycles, counts should be checked every 3 – 4 days for thrombocytopenia and for neutropenia during this time. Upon resolution to eligibility criteria, the patient may resume the subsequent cycle reduced by one dose level. If the toxicity recurs, the patient may resume treatment at the currently assigned dose with a change in the schedule to weekly dosing for 3 weeks followed by a 1 week rest.

6.1.4 Patients who experience Grade 4 anemia that is at least possibly attributable to selinexor must be removed from protocol therapy.

6.1.5 If toxicity does not resolve to meet starting parameters (section 5.2) within 21 days after the planned start of the next treatment cycle, the patient must be removed from protocol therapy.

6.1.6 If dose-limiting hematological toxicity recurs in a patient who has resumed treatment at Dose Level -1 and is already on the modified selinexor dosing schedule (3 weeks on/1 week off), the patient must be taken off protocol therapy.

6.2 Dose Modifications for Non-Hematological Dose-Limiting Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.5.1, the treatment will be held. If the toxicity resolves to meet eligibility parameters or baseline within 14 days after the planned start of the next treatment cycle, the patient may resume treatment reduced by one dose level. If the toxicity recurs, the patient may resume treatment at the currently assigned dose with a change in the schedule to weekly dosing for 3 weeks followed by a 1 week rest. Dosing schedules modified for toxicity will not be re-escalated, even if there is minimal or no toxicity with the modified dose.

6.2.1.1 Note that patients who experience Grade ≥ 3 anaphylaxis should be permanently removed from protocol therapy and should not resume treatment.

6.2.2 If toxicity does not resolve to meet eligibility or baseline parameters within 21 days after the planned start of the next treatment cycle, the patient must be removed from protocol therapy.

6.2.3 If the same dose-limiting toxicity recurs in a patient who has resumed treatment at Dose Level -1 and is already on the modified selinexor dosing schedule (3 weeks on/1 week off), the patient must be taken off protocol therapy.

6.3 Dose Modifications for Anorexia/Weight Loss

6.3.1 Anorexia and weight loss are anticipated toxicities and should be proactively managed. If a patient experiences Grade 3 anorexia or weight loss, dosing should continue as planned and maximal supportive care (e.g. appetite stimulants, nutritional supplements, tube feeding) should be implemented as outlined in Section 7.3.1.

6.4 Dose Modifications for Nausea/Vomiting/Dehydration

If a patient experiences Grade 3 nausea, vomiting, or dehydration, the treatment will be held. Patients should be treated with anti-emetic therapy as outlined in Section 7.3.2. If toxicity resolves to Grade ≤ 2 nausea/vomiting/dehydration within 3 days, drug may resume at same dose. Grade 3 nausea, vomiting, or dehydration that persists ≥ 3 days will be considered dose-limiting and require dose modification per Section 6.2.

6.5 Dose Modifications for Diarrhea

Grade	Action	Dose Modification
Grade 1	• Dietary recommendations: avoid lactose containing foods, apple juice	Maintain dose.
Grade 2	• Dietary recommendations: avoid lactose containing foods, apple juice, "BRAT" diet • Rule out other causes of diarrhea, including infectious agents. In case of opportunistic infection, withdraw all steroids (with tapering if medically appropriate) until culture is negative. • Institute standard anti-diarrheal therapy with loperamide (see Appendix X) • After the first occurrence of diarrhea, loperamide can be considered prophylactically approximately 1 – 2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours	Maintain dose.
Grade 3/4	• Dietary recommendations: avoid lactose containing foods, apple juice, "BRAT" diet • Rule out other causes of diarrhea, including infectious agents. In case of opportunistic infection, withdraw all steroids (with tapering if medically appropriate) until culture is negative • Institute standard anti-diarrheal therapy with loperamide (see Appendix X) • After the first occurrence of diarrhea, loperamide should be considered prophylactically approximately 1 – 2 hours before the administration of selinexor and repeat every 4 hours for the first 12 hours	Hold selinexor until Grade ≤ 2. If > 7 days, resume at lower dose level.

If a patient experiences Grade ≥ 3 diarrhea, treatment will be held. If diarrhea resolves to Grade ≤ 2 within 7 days, the drug may be resumed at the same dose. Grade ≥ 3 diarrhea that persists ≥ 7 days will be considered dose-limiting and require dose modification per Section 6.2. If Grade ≥ 3 diarrhea recurs at the lower dose and persists ≥ 7 days despite maximal use of antidiarrheal therapy, the patient will be removed from protocol therapy.

6.6 Dose Modifications for Hyponatremia

Grade	Action	Dose Modification
Grade 1 130 mmol/L to <LLN	• Be certain sodium level is corrected for hyperglycemia (serum glucose > 150 mmol/L).	Maintain dose.

	• Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). • Consider salt supplementation one – two times per day.	
129 – 126 mmol/L (asymptomatic)	• Be certain sodium level is corrected for hyperglycemia (serum glucose > 150 mmol/L). • Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). • Initiate salt supplementation two-three times per day.	Hold selinexor until Grade ≤ 1, resume at same dose level.
≤ 125 mmol/L or any symptomatic Grade 3	• Correct sodium as per institutional guidelines • Initiate salt supplementation two-three times per day.	Hold selinexor until Grade ≤ 1, resume at lower dose level.

6.7 Dose Modifications for Hepatic Adverse Events

6.7.1 If a patient experiences Grade ≥ 2 total bilirubin increase, treatment will be held. If toxicity resolves to Grade ≤ 1 within 7 days, the drug may be resumed at the same dose. Grade ≥ 2 total bilirubin increase that persists ≥ 7 days will be considered dose-limiting and require dose modification per Section 6.2.

6.7.2 If a patient experiences Grade ≥ 3 ALT or AST, treatment will be held. If toxicity resolves to Grade ≤ 1 within 7 days, the drug may be resumed at the same dose. Grade ≥ 3 ALT or AST that persists ≥ 7 days will be considered dose-limiting and require dose modification per Section 6.2.

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 protocol therapy.

7.3 Supportive Care

Clinical observations in over 400 adult patients treated with selinexor have indicated that the dose limiting toxicities (DLTs) are primarily related to anorexia, fatigue, nausea, vomiting, and diarrhea and with poor caloric and fluid intake leading to dehydration and weight loss. Significant fatigue and somnolence have also been noted in pediatric studies. Prophylactic use of 5-HT3 anti-nausea / antiemetic therapy is strongly recommended, and

further supportive care with acid suppression (proton pump inhibitors and/or H2-blockers), glucocorticoids, and other standard treatments should be administered as per institutional guidelines for symptomatic patients, keeping in mind that nausea and vomiting related to selinexor is often delayed.

Below are recommendations based on the experience of the adult clinical trials and the DFCI pediatric leukemia trial but do not represent required treatment approaches should the toxicities occur. The administration of supportive care is as per institutional guidelines and the treating provider.

7.3.1 Anorexia/Weight loss

Selinexor treatment can lead to anorexia, decreased food intake with subsequent weight loss. Participants should be weighed at least weekly during study-required outpatient visits during cycle 1 and biweekly during cycles 2 and 3. If the patient is admitted for dehydration or malnutrition, more frequent weight assessment is recommended. It is strongly recommended that patients receive ongoing nutritional assessment and dietary support consultation. Administration of high caloric beverages (e.g., Pediasure®) should be considered for all patients. The use of supplemental tube feeding is acceptable.

Patients who experience decreased food/liquid/caloric intake secondary to anorexia should have a patient log of food and drink with monitoring by the treatment team. Fresh juices, simple carbohydrates, as well as ginger-containing foods and beverages can improve appetite.

Supportive care should be escalated for ≥ Grade 1 anorexia or weight loss. **Guidelines for standard appetite stimulants are provided in the table below. The use of low dose olanzapine has been the most helpful in the control of nausea and anorexia in adult studies using selinexor.** Olanzapine for appetite stimulation and the treatment of chemotherapy induces nausea and vomiting, has not been thoroughly studied in children, and may have overlapping side effects with selinexor, including sedation and dizziness. For pediatrics, the suggested starting dose of olanzapine is approximately 0.06 mg to 0.1 mg/kg for patients < 10 years, 1.25 mg PO qPM for patients 10 – 12 years old or 2.5 mg PO qPM for patients > 12 years old.[33] Patients who exhibit no response after 4 weeks, defined as no weight gain or further loss, may increase by 1.25 mg/day weekly to maximum 2.5 mg/day for children < 10 years, 5 mg/day for children ages 10 – 12, and 10 mg/day for children older than 12 years; use caution escalating olanzapine doses in patients younger than 10 years. Olanzapine may be given in combination with a corticosteroid. Either dexamethasone < 0.25 mg/kg daily (max dose: 10 mg) or prednisone < 0.5 mg/kg daily (max dose: 20 mg) is recommended on the days of, and 1 day after, selinexor dosing.

Additional recommended agents are megestrol acetate (10 mg/kg/dose by mouth once daily; max dose: 800 mg/day) or cyproheptadine at a dose of 0.25 mg/kg/day orally in two divided doses and as second line. Dronabinol has also shown some activity in both nausea/emesis and anorexia in patients treated with selinexor.

Anorexia or Weight Loss		
Grade	**Action**	**Dose Modification**
Grade 1	• Rule out other causes of anorexia.	Maintain dose.

	• Assess dietary options (e.g., try a variety of other foods). • Add high-calorie supplements (e.g., Pediasure®). • Consider adding olanzapine: the suggested starting dose of olanzapine is 0.06 mg to 0.1 mg/kg for patients < 10 years, 1.25 mg PO qPM for patients 10 – 12 years old or 2.5 mg PO qPM for patients > 12 years old.[33]	
Grade ≥ 2	• Rule out other causes of anorexia. • Assess dietary options (e.g., try a variety of other foods). • Add high-calorie supplements (e.g., Pediasure®). • Consider adding olanzapine: the suggested starting dose of olanzapine is 0.06 mg to 0.1 mg/kg for patients < 10 years, 1.25 mg PO qPM for patients 10 – 12 years old or 2.5 mg PO qPM for patients > 12 years old.[33] Patients who exhibit no response after 4 weeks may increase by 1.25 mg/day weekly to maximum 5 mg/day for children ages 10 – 12 and 10 mg/day for children older than 12 years; use caution escalating olanzapine doses in patients younger than 10 years. • Consider addition of < 0.25 mg/kg (max 10 mg/dose) dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor. • Consider megestrol acetate (10 mg/kg/dose by mouth once daily; max 800 mg/day) or cyproheptadine at a dose of 0.25 mg/kg/day orally in two divided doses • Consider anabolic steroids such as oxandrolone, or dronabinol or other cannabinoid, mainly for patients who can't tolerate steroids or at high risk to progress.	See Section 6.3

7.3.2 Nausea and Emesis

Prophylactic treatment of nausea and emesis is strongly recommended during Cycles 1 and 2 and will be required for any dose level with the suffix "A" (e.g. 1A, 2A). See https://childrensoncologygroup.org/downloads/COG_SC_CINV_Guidelines_Document_Feb_2018.pdf for COG-endorsed antiemetic guidelines. If not instituted prophylactically, antiemetic therapy should begin once there is any indication of nausea as outlined in Section 6.4.

7.3.2.1 *Acute Emesis (occurring within 24 hours of administration of selinexor)*
Acute emesis has not frequently occurred with selinexor, but has been reported. Selinexor associated nausea/emesis generally responds to D2-antagonists (e.g.hydroxyzine), 5-HT3 antagonists (e.g. ondansetron), or combinations of agents. 5-HT3 receptor antagonists all appear equally effective at preventing nausea/emesis at standard doses. The efficacy of 5-HT3 receptor antagonists is significantly improved when combined with glucocorticoids. As QTc prolongation is the main side effect, magnesium and potassium should be corrected prior to use.

Neurokinin-1 receptor antagonists (e.g., aprepitant) should be considered once uncontrolled emesis persists despite the use of the above recommended standard treatments. Neurokinin-1 receptor antagonists can be given with combination of dexamethasone and 5-HT3 receptor antagonists.

Additional treatment: Metoclopramide hydrochloride has been effective when given prior to meals (up to 4 times a day) in adult patients. Dronabinol has shown some activity in both nausea/emesis and anorexia in patients treated with selinexor. Lorazepam can be added to the combination treatment of 5-HT3 receptor antagonists and dexamethasone, e.g., at night, but has been less effective in selinexor associated nausea and emesis.

7.3.2.2 *Delayed Emesis (occurring greater than 24 hours after administration of selinexor)*

Selinexor is infrequently associated with delayed, resistant emesis. Many of the regimens associated with delayed emesis are classified as high-emetic risk, and professional guidelines recommend the use of an NK1 receptor antagonist (either NK-1 blockers e.g., aprepitant on days 1 to 3 or fosaprepitant on day 1 only), plus a glucocorticoid on days 1 to 4, along with a 5-HT3 receptor antagonist (particularly second generation agents) on day 1. This regimen is effective against both acute and delayed emesis.

Conventional antiemetics are more successful at preventing emesis than in preventing nausea, particularly delayed nausea. As previously noted, in adult studies, olanzapine given once daily (typically given at night to mitigate sedative effects) was effective in both antiemetic and nausea control. It may also be useful for management of breakthrough emesis, and to improve food intake in patients with anorexia. Olanzapine for the treatment of chemotherapy induced nausea and vomiting, has not been thoroughly studied in children, and may have overlapping side effects with selinexor, including sedation and dizziness. Guidelines for olanzapine use in pediatrics can be found in Section 7.3.1.

The following additional agents have been administered in the adult population: lorazepam, alprazolam, dopaminergic D2-antagonists (eg, prochlorperazine, thiethylperazine, haloperidol), or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist.

7.3.3 Diarrhea

Refer to Section 6.5.

7.3.4 Dysgeusia

Suggested foods that can reduce metallic taste include sour foods that are rich in citric acid like orange juice or vitamin C drops. Avoid sweets. Oral hygiene should be optimized.

7.3.5 Ophthalmic Toxicities

Some episodes of blurred vision in adult clinical studies of selinexor have responded to IV hydration and have been attributed to dehydration. Therefore, IV hydration to correct any clinical deficits should be considered for blurred vision.

For blurred vision that does not improve with hydration within 24 hours, or any other ophthalmic toxicity grade 2 or higher, assessment by an ophthalmologist is strongly recommended. As of June 19, 2020, 2 of 42 patients enrolled on ADVL1414 have reported a serious adverse event of grade 4 vision loss, both of whom had tumors affecting the optic chiasm in the setting of tumor progression. Blurred vision is a known side effect of selinexor and described as generally mild, not accompanied by objective changes on ophthalmologic exam and nearly always resolves. However, a contribution of selinexor to blurred vision cannot be ruled out.

7.3.6 Fatigue/Somnolence

Fatigue has been noted as an adverse effect of selinexor in adult studies, and more significant fatigue, accompanied by somnolence, has been noted in pediatric studies to date, potentially associated with cerebral edema.[31] Glucocorticoid premedication continued for 48 hours post-dosing has been an effective management to date. Consideration may also be given to the use of methylphenidate (Initial: 0.3 mg/kg/dose PO qAM. Maintenance: 0.3-1 mg/kg PO qAM; maximum daily dose: 60 mg/**day**).[34,35]

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can be used in the setting of Grade 4 neutropenia and thrombocytopenia. The Study Chair should be notified before growth factors are initiated.

7.5 Concomitant Medications

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary (see Section 7.3). Clinical evidence suggests that selinexor can be safely given with acetaminophen, but given the theoretical potential for GSH depletion, acetaminophen should not be taken within 2 hours of administration of selinexor, and it is *recommended* that the total daily dose of acetaminophen should not exceed 20 mg/kg (maximum 1 gram/day) on days of selinexor dosing.

7.6 Part C (HGG Surgical Expansion Cohort)

For HGG patients who temporarily discontinue protocol therapy to undergo scheduled tumor resection, therapy may not be restarted until wound healed (minimum 3 weeks) and until recovery to eligibility requirements (Section 4.0). Although patients will not be taking selinexor during the recovery period, platelets should be monitored as part of the twice weekly CBCs required during Cycle 1 as per Section 8.1, and platelets should be maintained at a safe level to prevent post-operative bleeding as per institutional standards. Failure to adequately recover from surgery within 6 weeks after surgery will require removal from protocol therapy.

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 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[8]	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Neurologic Exam	X	Weekly	X
Pregnancy Test[1]	X	End of Cycle 1[1]	Every other cycle x 2 then q 3 cycles [1]
Height, weight	X	Weekly	Every other week during cycles 2 and 3 then prior to each cycle
BSA	X		X
Performance Status	X		
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[2]	Weekly[2]
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X
Creatinine, ALT, AST, bilirubin	X	Weekly	X
Albumin	X		X
Amylase, Lipase	X		X
Tumor Disease Evaluation	X	End of Cycle 1[9]	Every other cycle x 2 then q 3 cycles [3]
Patient Diary[4]		Weekly	X
Pharmacokinetics[5]	X	X	
Pharmacodynamic Studies[6]	X	X	
Tissue Studies[7] (Part C)	X		
Snellen Eye Chart[10]	X		Every other cycle x 2 then q 3 cycles [10]

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

1 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use two effective methods of birth control- including a medically accepted barrier method of contraceptive method (e.g., male or female condom). Abstinence is an acceptable method of birth control. Pregnancy testing is required prior to tumor imaging per institutional guidelines.

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

3 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation

of either a PR or CR. 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.

[4] Patient diary (see Appendix VII) should be reviewed and uploaded into RAVE weekly during Cycle 1, and after completion of each treatment cycle.

[5] See Section 8.3 for timing of PK studies.

[6] In consenting patients. See Section 8.4 for timing of Pharmacodynamic studies.

[7] See Section 8.5 for details of tissue studies.

[8] Part C: Observations are required as scheduled during protocol treatment only; *i.e.* weekly labs and observations are not required during the "surgery window" and may be held until resuming protocol therapy.

[9] Patients in Part C who interrupt treatment of Cycle 1 due to required resection should have scans repeated prior to resuming protocol therapy.

[10] Snellen eye chart should be used to assess visual acuity. If a decline in visual acuity occurs or other visual symptoms occur, the patient should be referred to an ophthalmologist for an examination.

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response: Patients who respond (CR, PR, or MR) 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 LifeImage.

COG institutions that are not connected via the LifeImage can send the images on hard copy film, CD ROM, USB flash drive or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1414) 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 (Required)

8.3.1 Description of Studies and Assay
Pharmacokinetics (PK) will be performed to determine the PK of selinexor in children. Pharmacokinetic analysis will be conducted at a bioanalytical laboratory using a validated assay.

8.3.2 Sampling Schedule

Blood samples will be obtained at the time points specified in Appendix III and just before tumor resection for patients on part C.

8.3.3 Sample Collection and Processing Instructions

Blood samples (1 ml) will be collected in the provided Vacutainer K_2EDTA tubes. (Please note the provided tubes may be larger than the required blood volume per sample so should not be filled completely). Record the exact time that the sample is drawn along with the exact time that the drug is administered.

1. Invert the tube gently at least 8 to 10 times to ensure mixing of the K_2EDTA and blood.
2. Immediately after collection place K_2EDTA 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 separated by a well–formed polymer barrier.
4. Transfer the plasma sample equally, using a transfer pipette, into two pre-labeled LoBind™ Eppendorf protein tubes (Aliquot A and B). *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.*
    - The aliquot A sample should be ≥ 0.2 ml, so if total plasma sample is < 0.4 ml, place most of the sample in Aliquot A.
    - **Please be sure to parafilm the tops of the Eppendorf LoBind™ Protein Tubes**.
5. Immediately after transfer of the plasma to the pre-labeled LoBind™ Eppendorf protein tubes, freeze the plasma aliquots on dry ice, snap-freeze in liquid nitrogen, or place directly into a -80°C freezer. Store samples at -80°C until shipping.

8.3.4 Sample Labeling

Each tube must be labeled with the study ID number, the patient ID number, the nominal time the sample was drawn, the aliquot (A or B), and a barcode ID number. All information on the PK labels is pre-printed with the exception of the patient ID number, which the site must write on each label using a fine-tip permanent marker.

Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s) when shipped. Record the actual collection date and time associated with the scheduled collection time point. Any handwritten changes made to the pre-printed barcode labels will not be captured when the barcodes are scanned.

8.3.5 Sample Shipping Instructions: Batch and ship all Aliquots A for each patient together in the same shipment on dry ice to AIT Bioscience. Note: If samples for more than 1 patient are being shipped, samples must be grouped (e.g., separate boxes or paper sleeves for each patient). Retain Aliquot B samples until requested by study assigned Research Coordinator to be shipped.

Shipment notification with tracking number should be sent to [redacted] lab@karyopharm.com; samples@aitbioscience.com) and the study assigned Research Coordinator, along with a copy of the PK Study form.

8.4 Pharmacodynamics

8.4.1 Description of Studies: Plasma proteins analysis will be performed for the identification of predictive biomarkers of response to selinexor (Appendix IV-A). Whole blood RNA will be collected for gene expression analysis using quantitative PCR (Appendix IV-B).

8.4.2 Sampling Schedule
On cycle 1, day 1, samples will be collected pre- and 4 hours after dose is given in consenting patients.

8.4.3 Sample Collection and Handling Instructions
Blood samples (2-2.5 ml) will be collected. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.4.4 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 Correlative Study Form, which must accompany the sample(s).

8.4.5 Sample Processing and Shipping Instructions: Refer to Appendix IV-A and Appendix IV-B for sample processing and shipping details.

8.5 Tissue Studies (Part C only)

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

8.5.1 Description of Studies
Tissue will be collected from original diagnosis or most recent resection and the resection that occurs as part of Part C.

8.5.1.1 Pharmacokinetics: Levels of selinexor will be determined in the tumor as

well as in blood at the time of resection to calculate blood/tumor ratio.

8.5.1.2 Pharmacodynamics:

a. Immunohistochemistry studies will be performed on fixed tumor tissue from pre-treatment and post-treatment specimens. Targets for analysis include XPO1, XPO1 cargos (p53, IKB alpha, pRb, FOXO3A, Survivin), cell cycle regulating proteins (c-Myc, Cyclin B, Cyclin D, ERK1, AKT1), and cell viability and cell death markers (H&E, Masson's trichrome, KI67, cleaved Caspase 3, TUNEL, Bcl2, Mcl1, FAS, ARRDC3, p75 NGFR).

b. Quantitative PCR will be performed on pre- and post-treatment tumor specimens for the following: XPO1, cell viability and cell death markers (NFKB, IKB alpha, BID, PUMA, CHOP, BAX), and genes that are upregulated once XPO1 is inactivated (based on Karyopharm gene chip studies) (ARRDC3, NGFR, SLC family, PCLO).

8.5.2 Sample Collection, Handling, and Shipment

Tissue from the on-therapy resection will be preserved at the time of resection. Detailed instructions regarding collection, handling, and shipping of tissue samples are located in Appendix V.

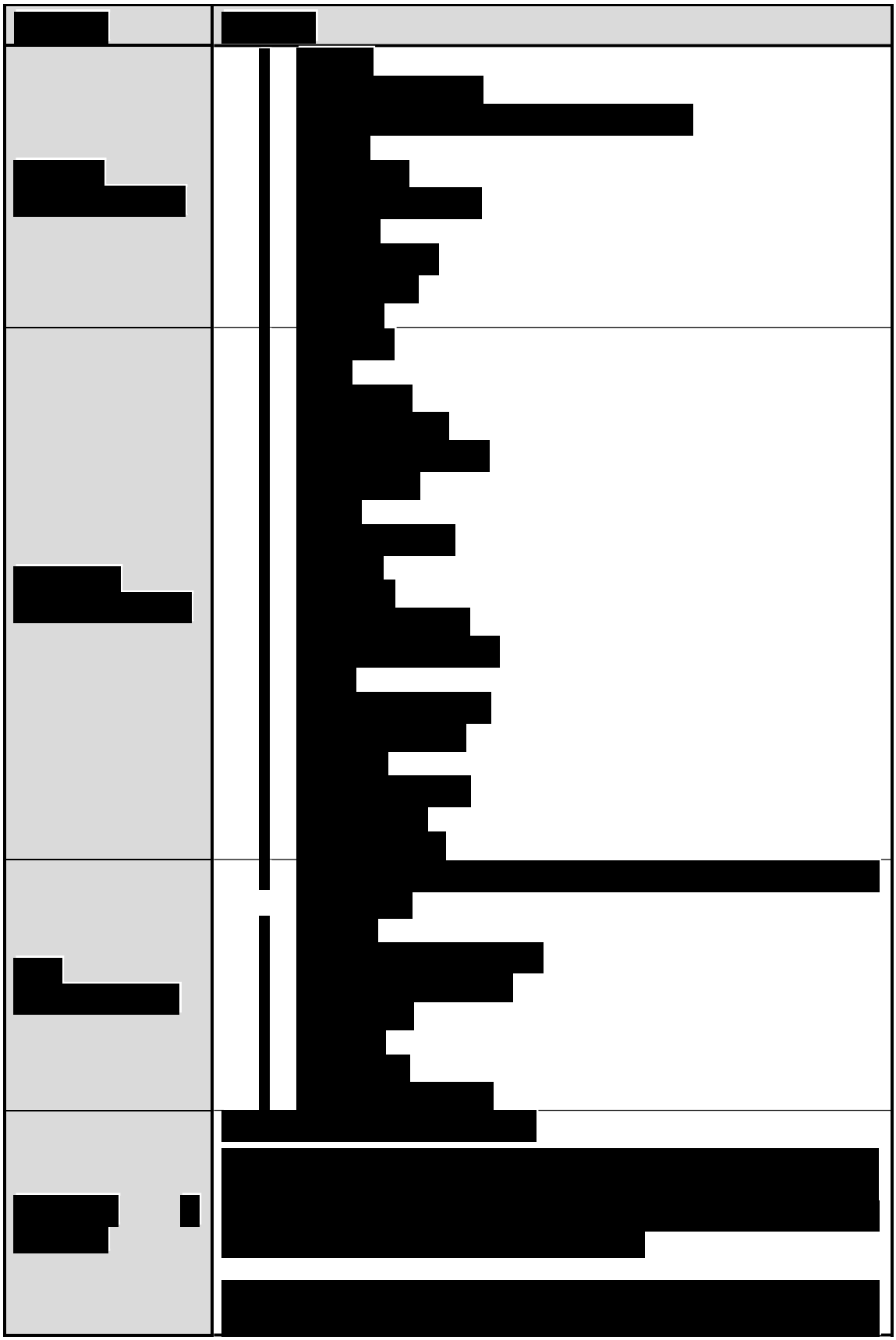
9.0 AGENT INFORMATION

9.1 Selinexor

(Xpovio™, KPT-330) NSC# 781780 [redacted]

[redacted]

[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 6.0).
c) Refusal of further 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 24 cycles
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 selinexor (See Section 8.1).
h) Failure to adequately recover from surgery within 6 weeks after surgery (patients in Part C)
i) Study is terminated by Sponsor.
j) 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 further required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study
f) The patient does not receive protocol treatment after study enrollment

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Strata:
Part A: Patients with relapsed or refractory solid tumors (Phase 1)
Part B: Patients with relapsed or refractory HGG (excluding DIPG) who do not require resection
Part C: Patients with relapsed or refractory HGG for whom resection is required

For Part A, a minimum of 2 evaluable patients with relapsed or refractory solid tumors including CNS tumors will be entered at each dose level for determination of MTD. Once the MTD or recommended Phase 2 dose has been defined, up to 6 additional patients with relapsed/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). A maximum of 29 patients is anticipated in this Part, assuming 6 evaluable patients are required for each dose level, 6 additional patients are needed 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 15-29 months. In the unlikely event that all dose levels require expansion to 12 patients per Section 11.2.2, then a maximum of 51 patients would be required allowing for a 20% inevaluable rate. This would require about 26-51 months for study completion.

With Amendment #1, an additional 29 patients is anticipated for Part A, assuming 6 evaluable patients are required for each dose level, 6 additional patients are needed for PK analysis, and a 20% inevaluable rate. The maximum accrual for the study (accounting for all parts of the study) will increase from 75 to 81 patients, assuming 20% inevaluability.

Amendment #4 will require a minimum of 4 evaluable patients. The maximum is expected to be 30 allowing for 6 patients at each of three dose levels, 6 for PK, and 20% inevaluability. This is expected to be completed within 15-30 months.

However, a dose level will be repeated with required maximal antiemetic therapy (5-HT3 antagonists and another antiemetic) prior to each dose during Cycles 1 and 2 if DLTs of vomiting or dehydration is experienced in ≥ 2/6 evaluable patients at a dose level. This condition would increase the expected maximum to 38 which allows for 12 patients at one dose level, 6 at the two other dose levels, 6 PK, and 20% inevaluability. This would be expected to be completed within 19-38 months.

In the unlikely event that all dose levels required expansion to 12 patients per Section 11.2.2, then the absolute maximum would be 68 patients. This includes 24 patients at a single dose level requiring expansion due to both 1) toxicities of different classes and 2) DLTs of vomiting or dehydration as well as 12 patients at each of the other two dose levels, 6 PK, and 20% inevaluability. This would be expected to be completed within 34-68 months.

The study has currently enrolled 31 patients (Fall 2019 SPR).

Non-Surgical Cohort (Part B): 10 evaluable patients with recurrent/progressive HGG (excluding DIPG) who do not require resection will be enrolled in a medical dose-expansion cohort (Part B) and will be treated at the MTD on the same schedule. If at any time greater than one out of three patients (or 33%) of the cohort of patients experience DLT, the cohort will be closed to further accrual. All patients enrolled on Part A who meet the eligibility criteria for Part B of the study who are evaluable for response as outlined in Section 11.2.3 of this protocol will be included in the evaluation rule.

Surgical Cohort (Part C): Up to 10 evaluable patients with recurrent/progressive HGG (excluding DIPG and disseminated tumors) for whom resection is recommended by their treating teams will be enrolled in a surgical dose-expansion cohort. These patients will be allowed to receive up to four doses of selinexor prior to resection. After their resection and when medically cleared, they will restart selinexor on the prior schedule. The purpose of this cohort will be to perform pharmacokinetic and pharmacodynamic studies on the tumor tissue, and to explore preliminarily the effectiveness of selinexor in this disease. If at any time greater than one out of three patients (or 33%) of the cohort of patients experience DLT, the cohort will be closed to further accrual.

Accrual to Parts B and C will only open once the MTD or recommended phase 2 dose has been determined in Part A, and may open concurrently with the PK expansion described above.

A maximum of 24 patients are expected to enroll in Parts B and C combined, assuming an inevaluability rate of 20%. We anticipate that each part of the study will require 6-12 months for enrollment.

Response for Part B will be defined as either MR, PR or CR on two consecutive 2D measurements on standard imaging done 4 weeks apart (See Section 12.6). Sustained responses are very rare in this cohort of recurrent non-DIPG HGGs. [36-38] We will consider the agent of sufficient interest for further evaluation in this disease category if at least one PR or CR, or at least two MRs, is observed among 10 enrolled patients. A response rate of 20% or more would be evidence of sufficient activity. If the true response rate is 20%, then the probability of observing one or more responses among 10 evaluable patients is about 89.3%. If the response rate is 5%, then the probability of observing at least one response is about 40.1%.

Clinical benefit for Part C will be evaluated separately using the criteria of no visible disease progression six months from the start of treatment. If two or more of a cohort of up to six patients are unable to resume therapy within 6 weeks after surgery, the surgical arm will be declared not feasible. If Part B has fully accrued, Part C will close to further accrual.

11.2 Definitions

11.2.1 Evaluable For Adverse Events

For all parts of the study, any patient who receives at least one dose of the study drug(s) and who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-escalation portion (Part A), during Cycle 1, patients must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. In Part A, patients who do not have DLT and do not receive at least 5 out of 6 of the prescribed doses (~85%) within the first cycle for reasons other than toxicities (e.g. progressive disease) will not be considered evaluable for toxicity and 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 (the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

11.2.3 Evaluability for Response

Any patient who is enrolled who meets eligibility criteria for Part B and receives at least one dose of selinexor will be considered evaluable for response provided: (1) the patient demonstrates progressive disease or death while on protocol therapy; or (2) the patient is observed on protocol therapy for at least one cycle and the tumor is not removed surgically prior to the time complete response or partial response is confirmed, or (3) the patient demonstrates a complete or partial response as confirmed according to protocol criteria. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule given in Section 11.1. All other patients will be considered non-responders. All patients considered to have a response (CR, PR, or MR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. See Section 8.2 regarding image submission instructions. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.3 Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study.[39] 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.

PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Hispanic or Latino		**Not Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	3	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	15	3	18
White	3	3	29	24	59
More Than One Race	0	0	0	0	0
Unknown	3	3	3	3	12
Total	6	6	47	33	92

11.5 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of selinexor 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 selinexor, 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, or the criteria specified in Section 12.6 for patients with CNS tumors, and will be reported descriptively.

Clinical benefit for Part B will be defined in one of two ways, either PR or CR on two consecutive 2D measurements on standard imaging (see Section 12.6) or as > 12 weeks from first dose without progressive disease, while clinical benefit in Part C will be defined as no visible disease progression six months from the start of treatment. Clinical benefit rate will be summarized separately for each of Parts B and C with 95% confidence intervals.

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

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).[40] 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 might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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 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 12.7.1 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 12.7.1 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

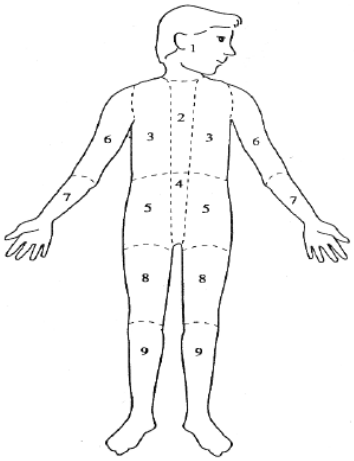
The response of MIBG lesions will be assessed on central review using the Curie scale[14] as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2.1 for details on transferring images to the Imaging Research Center.

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 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 5 in Section 12.8.1.

12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.5.1 Bone Marrow Involvement

Bone marrow obtained within 28 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 12.7.1.

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.
- **Minor Response (MR):** A greater than or equal to 25% but less than 50% reduction in the product of the greatest tumor diameter and its perpendicular diameter on MRI scan, on a stable or decreasing dose of steroids with a stable or improving neurologic examination.
- **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**
MR	CR, IR/SD	Any	No	**MR**
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 12.7.1 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 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.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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 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

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

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

12.7.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR, PR, or MR (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 data collection packet 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. 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.

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	

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.

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- 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 AND LYMPHATIC SYSTEM 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	Febrile neutropenia
EYE DISORDERS	Blurred vision
GASTROINTESTINAL DISORDERS	Constipation
GASTROINTESTINAL DISORDERS	Diarrhea
GASTROINTESTINAL DISORDERS	Dry mouth
GASTROINTESTINAL DISORDERS	Abdominal pain
GASTROINTESTINAL DISORDERS	Nausea
GASTROINTESTINAL DISORDERS	Vomiting
GENERAL DISORDERS AND	Other, specify (asthenia)

ADMINISTRATION SITE CONDITIONS	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Peripheral edema
INFECTIONS AND INFESTATIONS	Other, specify
INFECTIONS AND INFESTATIONS	Sepsis
INVESTIGATIONS	Creatinine increased
INVESTIGATIONS	Weight loss
METABOLISM AND NUTRITION DISORDERS	Anorexia
METABOLISM AND NUTRITION DISORDERS	Dehydration
METABOLISM AND NUTRITION DISORDERS	Hyperglycemia
METABOLISM AND NUTRITION DISORDERS	Hypokalemia
METABOLISM AND NUTRITION DISORDERS	Hypomagnesemia
METABOLISM AND NUTRITION DISORDERS	Hyponatremia
NERVOUS SYSTEM DISORDERS	Dizziness
NERVOUS SYSTEM DISORDERS	Dysgeusia
NERVOUS SYSTEM DISORDERS	Headache
NERVOUS SYSTEM DISORDERS	Insomnia
PSYCHIATRIC DISORDERS	Confusion
RESPIRATORY, THORACIS AND MEDIASTINAL DISORDERS	Dyspnea

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) via the web at http://ctep.cancer.gov (email the ADVL1414 COG Study Assigned Research Coordinator 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 NCI's Adverse Event Expedited Reporting System (CTEP-AERS) that can be found at http://ctep.cancer.gov.

An CTEP-AERS report must be submitted electronically via the CTEP-AERS

Web-based application located at https://eapps-ctep.nci.nih.gov/ctepaers. If prompted to enter a sponsor email address, please type in: PEPCTNAERS@childrensoncologygroup.org.

Email supporting documentation to the ADVL1414 COG Study Assigned 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 data submission 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 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 data form 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 treatment for cancer on trials.

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.

All secondary malignancies that occur following protocol treatment 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, Fetal Death, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and emailed along with any additional medical information to the ADVL1414 COG Study Assigned Research Coordinator. 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, along with the source of exposure (mother, father, breastfeeding).

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"** 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 expeditiouslyd 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 patient pregnancy or pregnancy in partners of men as a Grade 5 event as 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.

13.7.4 Abuse, Misuse or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects. A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use. All occurrences of abuse, misuse, or medication error with any study treatment are to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the abuse, misuse, or medication error. If the abuse, misuse, or medication error is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

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 Access to Rave for Data Submission/ Data Reporting

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

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-

5923 or by e-mail at ctsucontact@westat.com.

14.3 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

14.4 Data and Safety Monitoring Plan

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

14.4.1 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 chair 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.

14.4.2 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.

REFERENCES

1. Sharpless NE, DePinho RA: Cancer biology: gone but not forgotten. Nature 445:606-7, 2007
2. Turner JG, Dawson J, Sullivan DM: Nuclear export of proteins and drug resistance in cancer. Biochem Pharmacol 83:1021-32, 2012
3. Xu D, Grishin NV, Chook YM: NESdb: a database of NES-containing CRM1 cargoes. Mol Biol Cell 23:3673-6, 2012
4. Siddiqui N, Borden KL: mRNA export and cancer. Wiley Interdiscip Rev RNA 3:13-25, 2012
5. Huang WY, Yue L, Qiu WS, et al: Prognostic value of CRM1 in pancreas cancer. Clin Invest Med 32:E315, 2009
6. Noske A, Weichert W, Niesporek S, et al: Expression of the nuclear export protein chromosomal region maintenance/exportin 1/Xpo1 is a prognostic factor in human ovarian cancer. Cancer 112:1733-43, 2008
7. Shen A, Wang Y, Zhao Y, et al: Expression of CRM1 in human gliomas and its significance in p27 expression and clinical prognosis. Neurosurgery 65:153-9; discussion 159-60, 2009
8. van der Watt PJ, Maske CP, Hendricks DT, et al: The Karyopherin proteins, Crm1 and Karyopherin beta1, are overexpressed in cervical cancer and are critical for cancer cell survival and proliferation. Int J Cancer 124:1829-40, 2009
9. Yao Y, Dong Y, Lin F, et al: The expression of CRM1 is associated with prognosis in human osteosarcoma. Oncol Rep 21:229-35, 2009
10. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2009. CA Cancer J Clin 59:225-49, 2009
11. Smith MA, Seibel NL, Altekruse SF, et al: Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 28:2625-34, 2010
12. Green AL, Ramkissoon SH, McCauley D, et al: Preclinical antitumor efficacy of selective exportin 1 inhibitors in glioblastoma. Neuro Oncol, 2014
13. Houghton PJ, Kang M, Reynolds PC, et al: Preclinical Testing Program (PPTP) Stage 1 Evaluation of the XPO1/CRM1 Inhibitor KPT-330. Proceedings of the AACR LB-354 2013
14. Attiyeh E, McKeon-Fish A, Trillo R, et al: Inhibition of Exportin 1 (XPO 1) potently suppresses growth of human neuroblastoma cell lines. AACR: Pediatric Cancer at the Crossroads:Poster B36, 2013
15. Etchin J, Sanda T, Mansour MR, et al: KPT-330 inhibitor of CRM1 (XPO1)-mediated nuclear export has selective anti-leukaemic activity in preclinical models of T-cell acute lymphoblastic leukaemia and acute myeloid leukaemia. Br J Haematol 161:117-27, 2013
16. Etchin J, Sun Q, Kentsis A, et al: Antileukemic activity of nuclear export inhibitors that spare normal hematopoietic cells. Leukemia 27:66-74, 2013
17. KPT-330 Investigational Brochure v8.0, in Therapeutics K (ed), 2018
18. Development Safety Update Report, in NPM Pharma I (ed), 2013
19. Mau-Soerensen M, Razak ARA, Shields AF, et al: A first-in-class, first-in-human phase I trial of KPT-330 (selinexor), a selective inhibitor of nuclear export (SINE) in patients (pts) with advanced solid tumors. ASCO Meeting Abstracts 32:2537, 2014
20. Gounder MM, Loong HHF, Nyquist-Schultz K, et al: A phase 1b food effect study of the first-in-class, oral, selective inhibitor of nuclear export (SINE) selinexor (KPT-330) in patients (pts) with advanced sarcomas. ASCO Meeting Abstracts 32:10587, 2014
21. Martignetti J, Razak ARA, Chen Y, et al: Preclinical and early clinical activity of the oral selective inhibitor of nuclear export (SINE) exportin 1 (XPO1) antagonist KPT-330 (Selinexor) in patients (pts) with platinum-resistant/refractory ovarian cancer (OvCa). ASCO Meeting Abstracts 32:5522, 2014
22. Gutierrez M, Goy A, Byrd JC, et al: A phase 1 dose-escalation study of the oral selective inhibitor of nuclear export (SINE) KPT-330 (selinexor) in patients (pts) with heavily pretreated non-Hodgkin lymphoma (NHL). ASCO Meeting Abstracts 32:8518, 2014
23. Kuruvilla J, Gutierrez M, Shah B, et al: Preliminary Evidence Of Anti Tumor Activity Of Selinexor

(KPT-330) In a Phase I Trial Ofa First-In-Class Oral Selective Inhibitor Of Nuclear Export (SINE) In Patients (pts) With Relapsed / Refractory Non Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL) ASH Annual Meeting and Exposition:Abstract 90, 2013

24. Savona M, Garzon R, de Nully Brown P, et al: Phase I Trial of Selinexor (KPT-330), A First-In-Class Oral Selective Inhibitor Of Nuclear Export (SINE) In Patients (pts) With Advanced Acute Myelogenous Leukemia (AML) ASH Annual Meeting and Exposition:Abstract 1440, 2013
25. Yee KWL, Savona M, Sorensen M, et al: A phase 1 dose-escalation study of the oral selective inhibitor of nuclear export (SINE) KPT-330 (selinexor) in patients (pts) with relapsed/refractory acute myeloid leukemia (AML). ASCO Meeting Abstracts 32:7032, 2014
26. FDA grants accelerated approval to selinexor for multiple myeloma, U.S. Food & Drug Administration, 2019
27. Lassman AB, Wen PY, Bent MJVD, et al: Efficacy and safety of selinexor in recurrent glioblastoma. Journal of Clinical Oncology 37:2005-2005, 2019
28. Razak AR SM, Mahipal A, Shacham S, Yau CYF, Lassen UN, et al. : First-in-class, first-in-human phase I trial of KPT-330, a selective inhibitor of nuclear export (SINE) in patients (pts) with advanced solid tumors. . J Clin Oncol 2013;31((suppl; abstr 2505)). 2013
29. Lassman AB, Bent MJVD, Wen PY, et al: OS07.5 Interim analysis data from Phase 2 study on efficacy, safety & intratumoral pharmacokinetics of oral Selinexor (KPT-330) in patients with recurrent glioblastoma (GBM). Neuro-Oncology 19:iii14-iii14, 2017
30. Place AE, Blonquist TM, Stieglitz E, et al: Phase I Study of the Selinexor in Relapsed/Refractory Childhood Acute Leukemia. Blood 132:1405-1405, 2018
31. Alexander TB, Lacayo NJ, Choi JK, et al: Phase I Study of Selinexor, a Selective Inhibitor of Nuclear Export, in Combination With Fludarabine and Cytarabine, in Pediatric Relapsed or Refractory Acute Leukemia. J Clin Oncol 34:4094-4101, 2016
32. Development Safety Update Report, in NPM Pharma (ed), 2013
33. Flank J, Schechter T, Gibson P, et al: Olanzapine for prevention of chemotherapy-induced nausea and vomiting in children and adolescents: a multi-center, feasibility study. Support Care Cancer 26:549-555, 2018
34. Chin WC, Huang YS, Chou YH, et al: Subjective and objective assessments of sleep problems in children with attention deficit/hyperactivity disorder and the effects of methylphenidate treatment. Biomed J 41:356-363, 2018
35. Golubchik P, Levy T, Weizman A: The effect of methylphenidate treatment on psychopathic behavior of patients having attention-deficit hyperactivity disorder with and without oppositional defiant disorder. Int Clin Psychopharmacol 33:330-333, 2018
36. Fouladi M, Stewart CF, Blaney SM, et al: A molecular biology and phase II trial of lapatinib in children with refractory CNS malignancies: a pediatric brain tumor consortium study. J Neurooncol 114:173-9, 2013
37. Gururangan S, Chi SN, Young Poussaint T, et al: Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study. J Clin Oncol 28:3069-75, 2010
38. Warren KE, Gururangan S, Geyer JR, et al: A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: a Pediatric Brain Tumor Consortium study. J Neurooncol 106:643-9, 2012
39. Skolnik JM BJ, Jayaraman B, Patel D, Adamson PC. : Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol. 2008 Jan 10;26(2):190-5., 2008
40. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009

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	Appx.	Tube Type	Blood Volume per Sample	Cycle 1 Volume
Pharmacokinetics (Parts A and B)	III	Lavender Top	1 mL	**9 mL**
Pharmacokinetics (Part C)	III	Lavender Top	1 mL	**10 mL**
PD- Plasma Proteins	IV-A	Lavender Top	2 mL	**4 mL**
PD- Whole Blood	IV-B	PAXgene tube	2.5 mL	**10 mL**
Total Blood Volume –Cycle 1 (Parts A and B)				**23 mL**
Total Blood Volume –Cycle 1 (Parts C)				**24 mL**
Tumor Tissue (Part C)	V			

APPENDIX III: PHARMACOKINETIC STUDY FORM

COG Pt ID # _____ ACC # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Dose Level: _____mg/m^2 Dose Administered: _____mg

Plasma samples (1 mL) will be collected for pharmacokinetic studies at the time points listed in the table below. Record the exact date and time each sample is drawn and the time of the selinexor administration. In the event the dose is vomited within 30 minutes after administration on Cycle 1, Day 1 **and** there is no visible evidence of the tablet, the PK samples #2-9 should be collected after the second dose on Cycle 1, Day 3.

Blood Sample No.	Barcode # (from Sample Label)	Time Point	Scheduled Sample Collection Time	Scheduled Selinexor Time Point	Actual Date Sample Collected or Dose Given	Actual Time Sample Collected or Dose Given (24-hr clock)
1		**Cycle 1, Day 1**	**Prior to Dose on Cycle 1, Day 1**		___/___/___	____ : ____
				Cycle 1, Day 1	___/___/___	____ : ____
2		**Cycle 1, Day 1**	30 min. after Day 1 dose		___/___/___	____ : ____
3		**Cycle 1, Day 1**	1 hour after Day 1 dose		___/___/___	____ : ____
4		**Cycle 1, Day 1**	2 hour after Day 1 dose		___/___/___	____ : ____
5		**Cycle 1, Day 1**	3 hour after Day 1 dose		___/___/___	____ : ____
6		**Cycle 1, Day 1**	4 hour after Day 1 dose		___/___/___	____ : ____
7		**Cycle 1, Day 1**	6 hour after Day 1 dose		___/___/___	____ : ____
8		**Cycle 1, Day 1**	8 hour after Day 1 dose		___/___/___	____ : ____
9		**Cycle 1, Day 2**	24 (± 2) hr after Day 1 dose		___/___/___	____ : ____

Part C: An additional PK sample will be collected after 2 doses prior to Tumor Resection. Surgical resection should occur after dose on Day 8 but before dose on Day 15 of Cycle 1.

Blood Sample No.	Barcode # (from Sample Label)	Time Point	Scheduled Sample Collection Time	Scheduled Tumor Resection Date	Actual Date Sample Collected or Date of Resection	Actual Time Sample Collected or Dose Given (24-hr clock)
10		After 2 doses	**Prior to Tumor Resection**		___/___/___	____ : ____
				___/___/___	___/___/___	____ : ____

Refer to Section 8.3 processing and shipping details. One copy of this Pharmacokinetic Study Form should be uploaded into RAVE.

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: _____

APPENDIX IV-A: PHARMACODYNAMICS STUDY FORM- PLASMA PROTEINS

COG Pt ID # _____ ACC # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Dose Level: _____mg/m^2 Dose Administered: _____mg

Plasma samples (2 mL) will be collected for Plasma Protein studies on cycle 1, day 1, pre- and 4 hours after dose is given in consenting patients. Record the exact date and time each sample is drawn and the time of the selinexor administration.

Blood Sample No.	Time Point	Scheduled Sample Collection Time	Scheduled Selinexor Time Point	Actual Date Sample Collected or Dose Given	Actual Time Sample Collected or Dose Given (24-hr clock)
1	**Cycle 1, Day 1**	**Prior to Dose on Cycle 1, Day 1**		___/___/___	|__|__| : |__|__|
			Cycle 1, Day 1	___/___/___	|__|__| : |__|__|
2	**Cycle 1, Day 1**	**4 hr after Day 1 dose**		___/___/___	|__|__| : |__|__|

Sample Processing Procedures:

1. Ensure all tubes are labeled appropriately with site number, patient number and initials, and collection date prior to collection. Use a fine-point black permanent marker or lab marker to label tubes.
2. Collect 2 ml of blood into one BD Vacutainer tube for each time point. Be sure to use the correct tube for each time point.
3. Invert sample at least 8 to 10 times to ensure mixing of the EDTA and blood.
4. Immediately after collection place EDTA tube on ice or at 4°C for no longer than 30 minutes.
5. Centrifuge tube within 30 minutes of collection at 1000 g for 10 minutes at 4°C until red cells and plasma are separated by a well–formed polymer barrier.
6. Transfer the plasma sample equally, using a transfer pipette, into two cryogenic vials (Aliquot A and B). *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.*
7. Immediately after transfer, the aliquots are stored at -70°C to -80°C.

Sample Shipping Instructions:

Batch and ship all Aliquots A for each patient together in the same shipment on dry ice to Karyopharm Therapeutics. Note: If samples for more than 1 patient are being shipped, samples must be grouped (e.g., separate boxes or paper sleeves for each patient). Retain Aliquot B samples until requested by Karyopharm Therapeutics to be shipped.

Shipment notification with tracking number should be emailed to lab@karyopharm.com and study assigned Research Coordinator along with a copy of this PD Study form.

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: _____

APPENDIX IV-B: PHARMACODYNAMICS STUDY FORM- WHOLE BLOOD RNA

COG Pt ID # _____ ACC # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Dose Level: _____mg/m^2 Dose Administered: _____mg

Whole blood RNA (two x 2.5 mL samples per time point) will be collected for gene expression analysis on cycle 1, day 1, pre- and 4 hours post dose administration. Record the exact date and time each sample is drawn and the time of the selinexor administration.

Blood Sample No.	Time Point	Scheduled Sample Collection Time	Scheduled Selinexor Time Point	Actual Date Sample Collected or Dose Given	Actual Time Sample Collected or Dose Given (24-hr clock)
1	**Cycle 1, Day 1**	**Prior to Dose on Cycle 1, Day 1**		___/___/___	|__|__| : |__|__|
			Cycle 1, Day 1	___/___/___	|__|__| : |__|__|
2	**Cycle 1, Day 1**	**4 hr after Day 1 dose**		___/___/___	|__|__| : |__|__|

Sample Processing Procedures:

1. Ensure PAXgene® Blood RNA Tube is at 18°C to 25°C prior to sample collection. To prevent contamination, the PAXgene® tube should be the last tube drawn for the correlative studies.
2. Allow at least 10 seconds for a complete blood draw to take place. Ensure that the blood has stopped flowing into the tube before removing the tube from the holder. The PAXgene® tube with its vacuum is designed to draw up to 2.5 mL of blood into one tube.
3. Collect 2.5 ml of blood into each of the two PAXgene® tubes required at every time point. Label tubes as Aliquot (A) and Aliquot (B).
4. Immediately after blood collection, gently invert the PAXgene® tube 8 – 10 times.
5. Store the PAXgene® tube upright at room temperature (18°C to 25°C) for a minimum of 2 hours and a maximum of 72 hours before transferring to a -20°C freezer.
6. When freezing samples, stand the PAXgene® tube upright in a wire rack. Do not freeze tubes upright in a styrofoam tray as this may cause the tubes to crack.
7. The PAXgene® tubes can be stored at -20°C and below. If tubes are to be kept at temperatures below -20°C, freeze them first at -20°C for 24 hours, then transfer them to -70°C or -80°C.

Sample Shipping Instructions:
Batch and ship all Aliquots A for each patient together in the same shipment on dry ice to Karyopharm Therapeutics. Note: If samples for more than 1 patient are being shipped, samples must be grouped (e.g., separate boxes or paper sleeves for each patient). Retain Aliquot B samples until requested by Karyopharm Therapeutics to be shipped.

Shipment notification with tracking number should be emailed to lab@karyopharm.com and study assigned Research Coordinator, along with a copy of this PD Study form.

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: _____

APPENDIX V: TISSUE STUDIES FORM (PART C ONLY)

COG Pt ID # _____ **ACC #** _____ **Date:**_____
(Please do not write patient names on this form or on samples)

Sample Labeling: Samples should be labeled with the following information:

Protocol number: **ADVL1414** Institution: _____ Sample Date: _____

Site of Acquired Tissue: _____

Tissue obtained at (check one option below): ☐Diagnosis ☐Relapse ☐Subsequent Resection/Biopsy

Tissue sample is from a: ☐Resection or ☐Biopsy

Tissue Type: ☐Fresh Frozen Tissue ☐Formalin Fixed Tissue
☐Paraffin Embedded Tissue Block ☐Unstained Slides

All blocks or slides must be labeled with the patient's study registration number (COG Patient ID #), the study I.D. (ADVL1414), and the sample collection date. Data should be recorded on this Tissue Studies Form, which must accompany the sample(s).

Archived Tissue Samples: Archived paraffin-embedded tissue must be available for any previous resections for that patient (approximately 20 unstained slides or tumor block). The blocks or slides of tumor material should be sent at room temperature via Federal Express. During the warmer months (June – August), it is advisable to ship the block(s) with a frozen gel ice-pack in order to prevent the melting of paraffin-embedded tissue blocks during transit. Ensure cold pack is not in direct contact with specimen.

Tumor Biopsy Collected at Surgical Resection
Tumor tissue will be obtained upon surgical resection during cycle 1 from Part C patients only. At least 500 mg of tumor tissue should be collected by standard surgical procedures. Approximately 0.5 ml will be fresh frozen with preservatives in 2 mL screw cap cryogenic vials, while the remainder will be preserved in 10% buffered formalin in 15 ml conical tubes.

a. **Fresh (flash frozen) biopsy** (approximately 0.5 ml collected). Please collect in the 2 mL screw cap cryogenic vials. Please do not fill tube more than ~1/3 full (~0.6 ml). Biopsy samples should be stored frozen at or below -70°C until shipment. Frozen samples will be shipped on dry ice.

b. **Formalin-fixed biopsy** (remainder of sample collected during surgery after collection of fresh non-preserved tissue). Biopsy samples that are fixed in 10% buffered formalin will be stored at 4°C at the study sites until shipment. Parafilm all tubes. Fixed samples will be batched and shipped at 4°C.

Please ship specimens along with email notification (with a copy to the Research Coordinator) of sample shipment and tracking number to:

• **Archived Tissue Samples** • **Formalin-Fixed Biopsy**	[redacted]
• **Fresh (flash frozen) Biopsy**	[redacted]

One copy of this form should be uploaded into RAVE. 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 collected samples)

APPENDIX VI: SELINEXOR DOSING NOMOGRAM

Selinexor Dose Assignment: 35 mg/m^2
(Dose Level -1)

BSA (m^2)	Total Daily Dose (mg/day)
0.84-0.92	30
0.93-1.07	35
1.08-1.21	40
1.22-1.35	45
1.36-1.5	50
1.51-1.64	55
1.65-1.78	60
1.79-1.92	65
1.93-2.07	70
2.08-2.21	75
≥ 2.22	80

Selinexor Dose Assignment: 45 mg/m^2
(Dose Level 1)

BSA (m^2)	Total Daily Dose (mg/day)
0.84-0.94	40
0.95-1.05	45
1.06-1.16	50
1.17-1.27	55
1.28-1.38	60
1.39-1.50	65
1.51-1.61	70
1.62-1.72	75
1.73-1.83	80
1.84-1.94	85
1.95-2.05	90
2.06-2.16	95
2.17-2.27	100
≥ 2.28	105

Selinexor Dose Assignment: 55 mg/m^2
(Dose Level 2)

BSA (m^2)	Total Daily Dose (mg/day)
0.84-0.86	45
0.87-0.95	50
0.96-1.04	55
1.05-1.13	60
1.14-1.22	65
1.23-1.31	70
1.32-1.4	75
1.41-1.5	80
1.51-1.59	85
1.6-1.68	90
1.69-1.77	95
1.78-1.86	100
1.87-1.95	105
1.96-2.04	110
2.05-2.13	115
2.14-2.22	120
≥ 2.23	125

APPENDIX VII: MEDICATION DIARY FOR SELINEXOR

COG Patient ID:_____ **Acc#**_____ **Institution :**_____

Please do not write patient names on this form.

Complete each day with the time and dose given for selinexor. If a dose is not due or is accidentally skipped leave that day blank. ***Make note of other drugs and supplements taken under the Comments section below***. Selinexor tablets should be swallowed whole. Selinexor should be taken with food. If a dose is vomited within 30 minutes of administration and there is visible evidence of the tablet, the dose should be repeated. If the tablet is not visible, or the dose is vomited later than 30 minutes after administration, the dose should not be repeated. The patient/caregiver should make a note of if there is visible evidence of tablet on the pill diary and proceed with the next dose at the next scheduled time of administration. Add the dates to the calendar below and return the completed diary to your institution after each treatment cycle.

EXAMPLE			***Number of Selinexor tablets***		***Comments***
	Date	***Time***	**10 mg**	**25 mg**	
Day 1	*1/15/14*	*8:30 AM*	2	1	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ Selinexor Dose: _____mg Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

Day	Date	Time	10 mg	25 mg	Comments
Day 1		**Selinexor: _____**			
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					
Day 8		**Selinexor: _____**			
Day 9					
Day 10					
Day 11					
Day 12					
Day 13					
Day 14					
Day 15		**Selinexor: _____**			
Day 16					
Day 17					
Day 18					
Day 19					
Day 20					
Day 21					
Day 22		**Selinexor: _____**			
Day 23					
Day 24					
Day 25					
Day 26					
Day 27					
Day 28					

APPENDIX VIII: 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 SGPT is 45 U/L regardless of baseline.

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

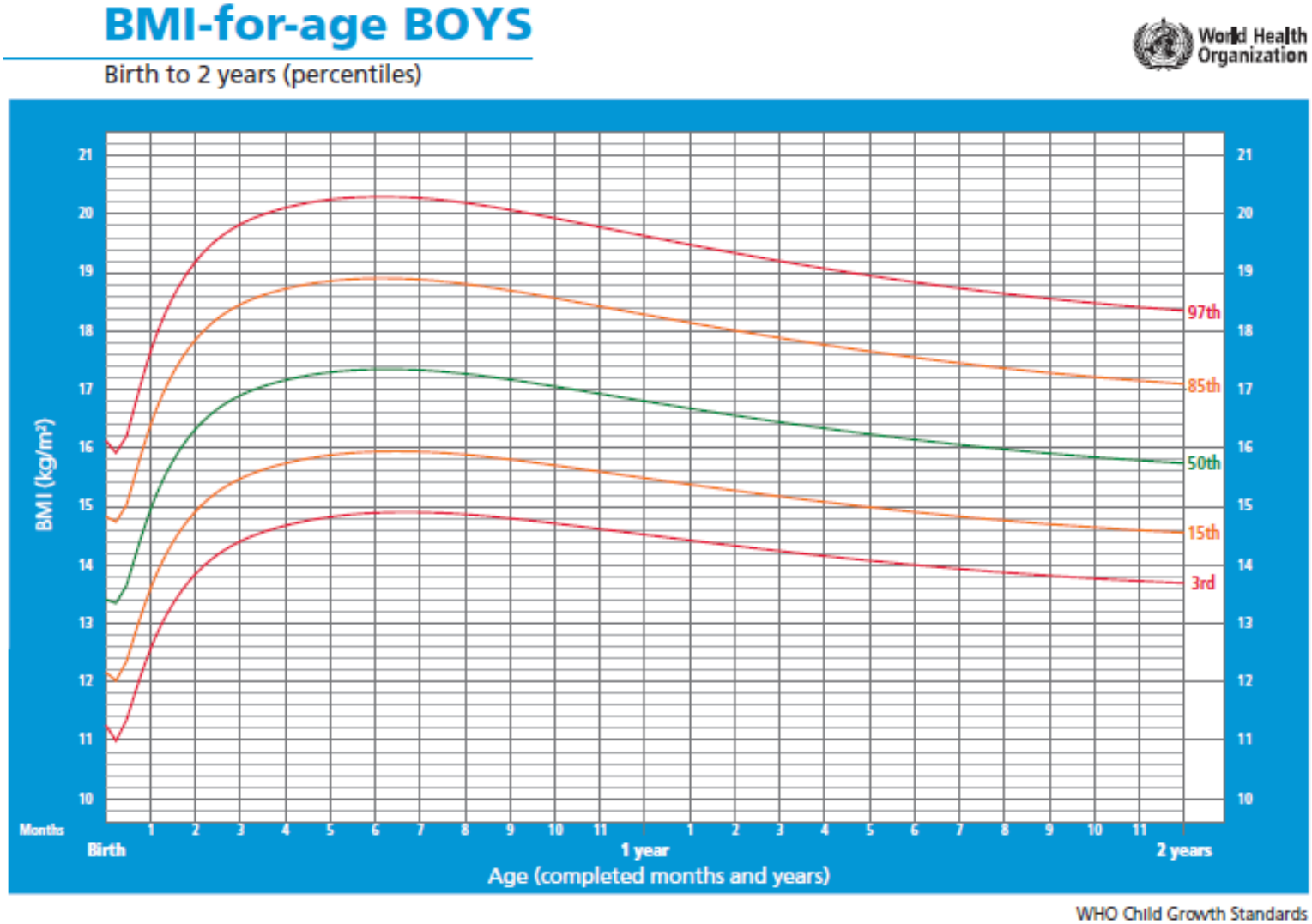
AST: For the purpose of this study, the ULN for SGPT is 50 U/L regardless of baseline.

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

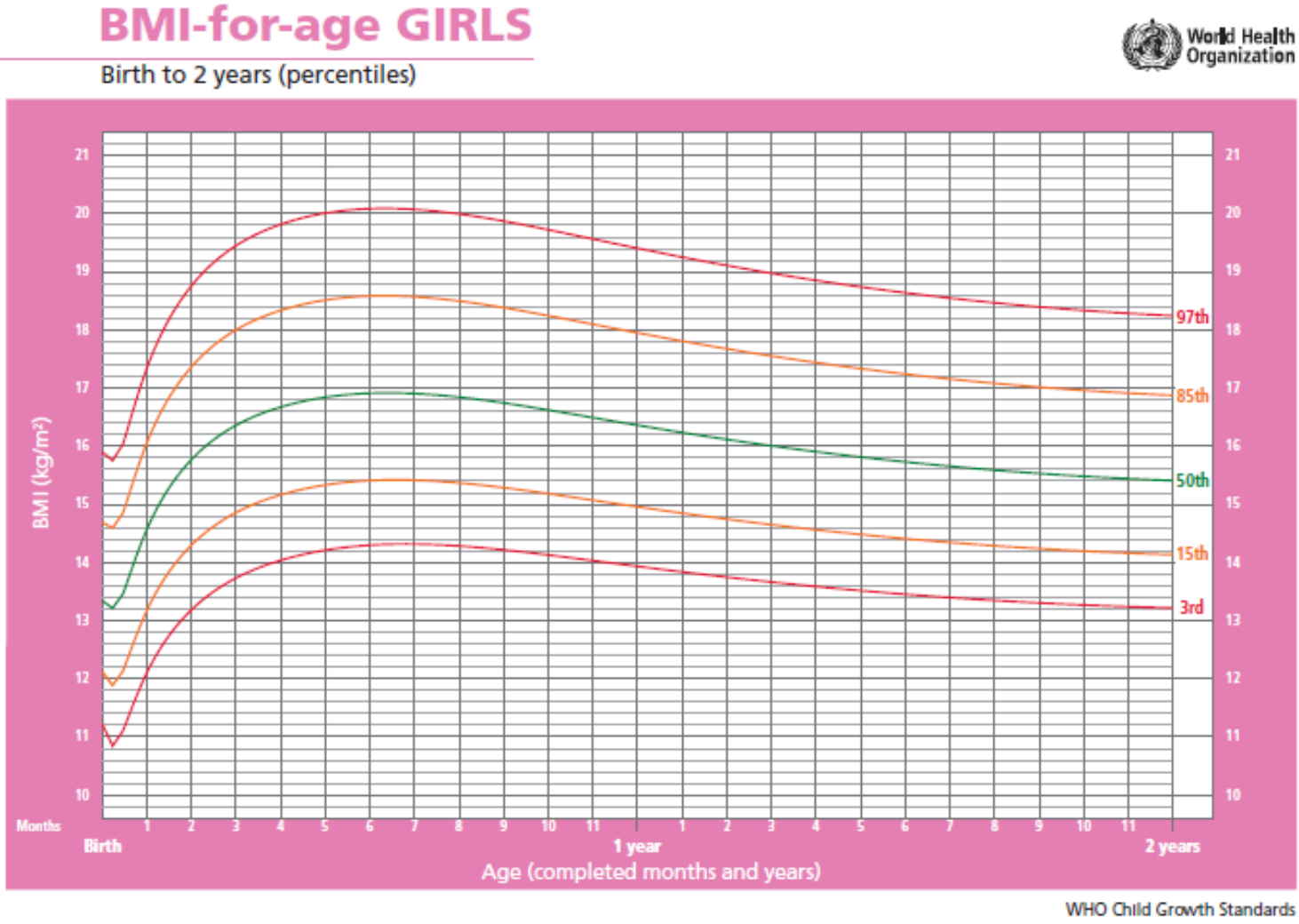
GGT:

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

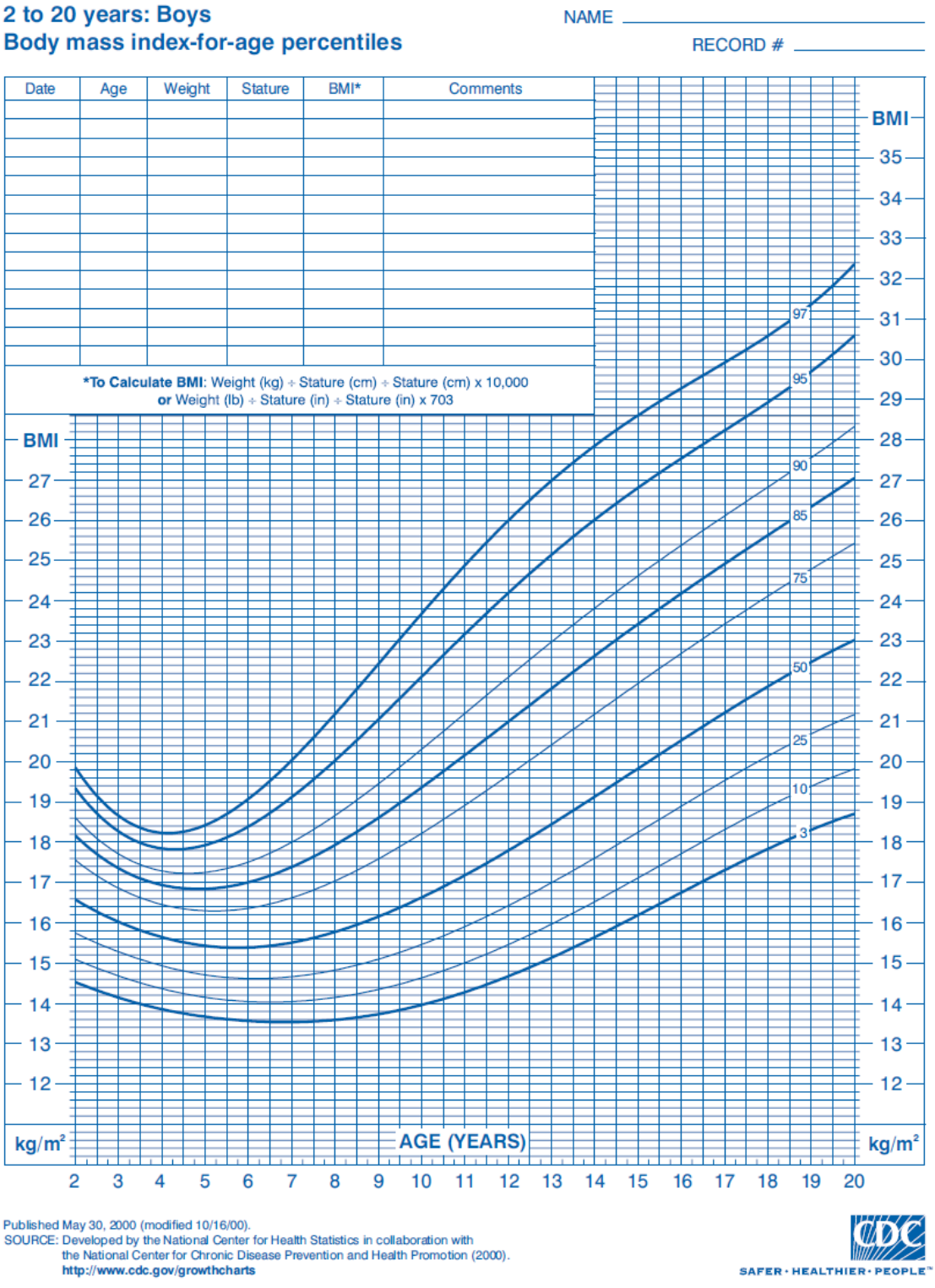
APPENDIX IX: BMI GROWTH CHARTS



APPENDIX IX: BMI GROWTH CHARTS, cont.

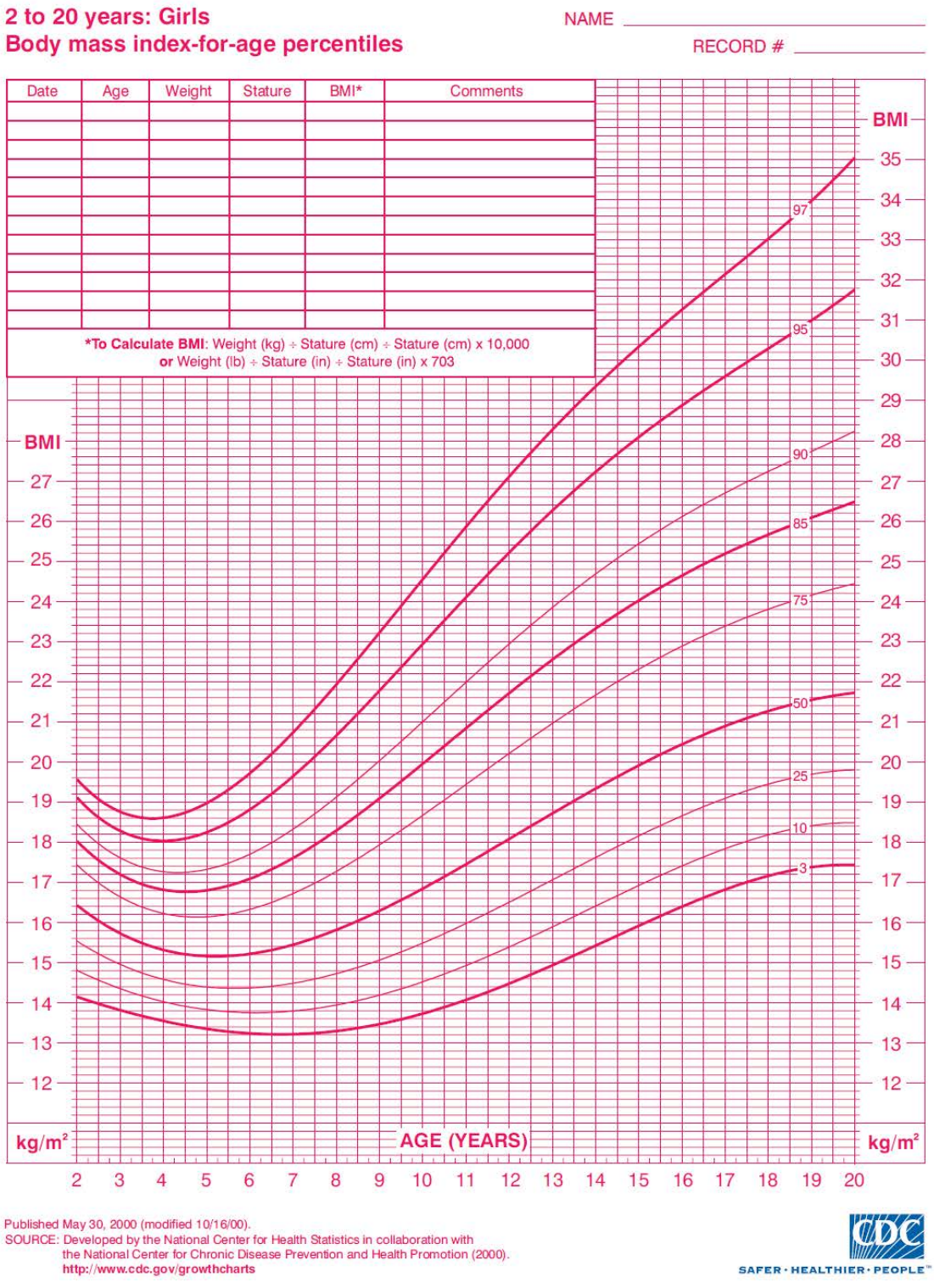


APPENDIX IX: BMI GROWTH CHARTS, cont.



*20 yr. cut-off should be used for patients 21 years old.

APPENDIX IX: BMI GROWTH CHARTS, cont.



*20 yr. cut-off should be used for patients 21 years old.

APPENDIX X: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

You should purchase or will be given a prescription for loperamide to have available to begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given **loperamide** based on body weight.

Be aware of your child's bowel movements. At the first sign they become softer than usual or if your child has any notable increase in the number of bowel movements over what is normal for him/her, begin taking loperamide (Imodium).

Please follow these directions carefully, using dosing guidelines below:

- Take _____ at the first sign of diarrhea.
- Continue taking _____ every __ hours until the diarrhea slows or the normal pattern of bowel movements returns. Repeat the same doses and frequency if the diarrhea returns.
- Do not exceed _____ in a 24 hour period.
- Please call your doctor if you have any questions about taking loperamide, if your child's diarrhea is not under control after two days, or if he/she is feeling extremely weak, lightheaded, or dizzy.
- Make an extra effort to give your child lots of fluids (several glasses of pedialyte, fruit juices, soda, soup, etc.) while your child is participating in this study.
- Side effects may include tiredness, drowsiness or dizziness. If your child experiences these side effects, or if your child is urinating less frequently than usual, please contact your child's physician.
- Do not give your child any laxatives without consulting with his/her physician.

LOPERAMIDE DOSING RECOMMENDATIONS (NOTE: maximum dose of loperamide for adults is 16 mg/day) *ALL patients: discontinue loperamide when the patient is no longer experiencing significant diarrhea.*	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg (20 mL or 4 teaspoonfuls) per day.
≥ 13 kg to < 20 kg	Take 1 mg (5 mL [1 teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 4 hours. Do not exceed 6 mg (30 mL or 6 teaspoonfuls) per day.
≥ 20 kg to < 30 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 8 mg (40 mL or 8 teaspoonfuls) per day.
≥ 30 kg to < 43 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 2 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 12 mg (60 mL or 12 teaspoonfuls) per day.
Over 43 kg	Take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 2 hours. During the night, the patient may take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg (80 mL or 16 teaspoonfuls) per day.

APPENDIX XI: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

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 at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval),

consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located 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

U.S. sites participating in the PEP-CTN network are required to use the NCI CIRB as of March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

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

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

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the Registration and Credential Repository (RCR) profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *COG*, and protocol number (*insert study number*).
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents

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

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

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

Checking Your Site's Registration Status

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

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

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

affiliated networks.

Requirements For ADVL1414 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, and/or Protocol Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

Data Submission / Data Reporting

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

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

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Data Quality Portal

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

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

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

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

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

APPENDIX XII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY
(for children from 7 through 12 years of age)

A study of selinexor in patients with recurrent and refractory solid tumors, including CNS tumors

1. We have been talking with you about taking part in a research study because you have cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer you have. We will do this by trying a new medicine to treat your cancer.

2. Children who are part of this study will be treated with a cancer fighting medicine called selinexor. You will have regular tests and exams done more often while you are in this study. The doctors want to see if selinexor will work well to get rid of your cancer. That is why we are doing this study.

3. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is selinexor may cause your cancer to shrink or go away but we don’t know for sure if there is any benefit of being part of the study.

4. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that you may have problems or side effects from selinexor. Other things may happen to you that we don’t yet know about.

5. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

6. If you decide to be treated with selinexor you will have some tests and check-ups done more often than you might if you weren’t part of the study. Some of these needed tests will require extra needle sticks to collect additional blood samples.

7. We are asking your permission to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. Some of these samples are collected when you may not need to have a blood sample taken and may require extra needle sticks. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY
(for teens from 13 through 17 years of age)

A study of selinexor in patients with recurrent and refractory solid tumors, including CNS tumors

1. We are asking you to take part in a research study because you have cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer you have. We will do this by trying a new medicine to treat your cancer.

2. Children and teens who are part of this study will be treated with a cancer fighting medicine called selinexor. You will have regular tests and exams done more often while you are in this study. The doctors want to see if selinexor will work well to get rid of your cancer. That is why we are doing this study.

3. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is selinexor may cause your cancer to shrink or go away but we don't know for sure if there is any benefit of being part of the study.

4. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have problems or side effects from selinexor. Other things may happen to you that we don't yet know about.

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7. We are asking your permission to collect additional blood. We want to see if there are ways to tell how the cancer will respond to treatment. Some of these samples are collected when you may not need to have a blood sample taken and may require extra needle sticks. You can still take part in this study even if you don't allow us to collect the extra blood samples for research.