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A PHASE I/II STUDY OF THE SELECTIVE INHIBITOR OF NUCLEAR EXPORT SELINEXOR (KPT-330) IN COMBINATION WITH FLUDARABINE AND CYTARABINE IN PEDIATRIC PATIENTS WITH REFRACTORY OR RELAPSED LEUKEMIA OR MYELODYSPLASTIC SYNDROME

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SELHEM: A PHASE I/II STUDY OF THE SELECTIVE INHIBITOR OF NUCLEAR EXPORT SELINEXOR (KPT-330) IN COMBINATION WITH FLUDARABINE AND CYTARABINE IN PEDIATRIC PATIENTS WITH REFRACTORY LEUKEMIA OR MYELODYSPLASTIC SYNDROME

Principal Investigator: Jeffrey E. Rubnitz, MD, PhD

Institution/Sponsor-IND holder: St. Jude Children's Research Hospital. IND# 122,979

Brief overview: Phase I/II study to characterize the toxicity profile and to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of selinexor when given with fludarabine and cytarabine in pediatric patients with relapsed or refractory hematologic malignancies including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), mixed phenotype acute leukemia (MPAL) and myelodysplastic syndrome (MDS).

Intervention: Interventional, primary therapeutic.

Drug: Selinexor

Drug: Fludarabine

Drug: Cytarabine

Procedure: LP with administration of ITHMA or cytarabine

Brief outline of treatment plan:

Selinexor will be given orally on days 1, 3, 8, 10, 22, and 24. The starting dose of Selinexor is 30 mg/m²/dose po given twice weekly and escalated or de-escalated based on tolerability.

Dose level	Selinexor (mg/m ² /dose on days 1, 3, 8, 10, 22, 24)	Fludarabine (mg/m ² /dose on days 16-20)	Cytarabine (g/m ² /dose on days 16-20)
-1	20	30	2
1	30	30	2
2	40	30	2
3	55	30	2
4	70	30	2

Fludarabine (30 mg/m²/dose IV over 30 minutes daily for 5 days) and **cytarabine** (2 gram/m²/dose IV over 4 hours daily for 5 days) will be given on days 16 through 20. Fludarabine and cytarabine may be given before day 15 if the treating physician, after consulting with the principal investigator (PI), believes it is in the patient's best interest based on disease progression.

Diagnostic lumbar puncture and intrathecal (IT) chemotherapy will be given prior to cycle 1. Patients without evidence of central nervous system (CNS) leukemia will receive no further IT therapy during cycle 1. Patients with CNS disease will receive weekly IT therapy (age-adjusted methotrexate, hydrocortisone, and cytarabine) until the cerebrospinal fluid (CSF) becomes free of leukemia (minimum of 4 doses). Bone marrow aspiration (BMA) and biopsy (if indicated) to assess response will be performed on days 15 and 29 of cycle 1. One cycle of therapy will be 42-56 days. Participants may receive one subsequent course of selinexor + fludarabine and cytarabine if there is no disease progression or unacceptable toxicity (maximum 2 courses). In addition, patients who demonstrated response to selinexor may receive selinexor alone in subsequent courses at the discretion of the treating physician, after consultation with the study PI; the selinexor may be continued indefinitely.

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Study design: Phase I/II study with include two phases. The dose-escalation phase will characterize the dose-limiting toxicities (DLTs) and determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of selinexor when given in combination with fludarabine and cytarabine. The RP2D will be chosen based on the MTD and totality of the data (clinical, PK, and PD data from this and other trials). The Phase II cohort will further assess the safety and will explore the efficacy of this combination.

Sample size: The sample size is determined by the number of DLTs observed at each dose level in each stratum. The minimum sample size is 6 and the maximum sample size is 24 evaluable patients for the dose escalation phase. Additionally, the phase II portion of the study will include a minimum of 28 and maximum of 39 evaluable patients.

Data management: Data management and statistical analysis will be provided locally by the Comprehensive Cancer Center Hematological Malignancies Program and the Biostatistics Department at St. Jude Children's Research Hospital.

Human subjects: The main risk to research participants will be the potential toxicities associated with the use of chemotherapy and the investigational agent, selinexor. The research participants will be informed of the toxicities that have been associated with the study drugs and potential side effects of procedures recommended in this study. Adverse events will be monitored, treated, and reported following institutional and federal guidelines and regulations.

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1.0 OBJECTIVES

1.1 Primary Objective

- 1.1.1 To determine a tolerable combination of selinexor, fludarabine, and cytarabine in pediatric patients with relapsed or refractory hematologic malignancies including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), mixed phenotype acute leukemia (MPAL) and myelodysplastic syndrome (MDS) in the phase I portion of the study.
- 1.1.2 To estimate the overall response rate, as defined by complete response or complete response with incomplete count recovery, of selinexor in combination with fludarabine and cytarabine for patients with relapsed or refractory AML in the phase II portion of the study.

1.2 Secondary Objectives

- 1.2.1 To characterize the pharmacokinetics of selinexor, when administered in tablet form, after the first dose and at steady-state, as well as in combination with fludarabine and cytarabine.

1.3 Exploratory Objectives

- 1.3.1 To characterize the pharmacodynamic and biological effects of selinexor and to search for biological predictors of response.

2.0 BACKGROUND AND RATIONALE

2.1 Background

The outcome for children with relapsed or refractory leukemia is very poor, necessitating the development of novel agents and effective salvage regimens. An attractive target is Exportin 1 (XPO1), also called chromosome region maintenance 1 (CRM1), a nuclear protein exporter that is a member of the karyopherin β family of transporters and is the primary nuclear exporter of key tumor suppressor and regulatory proteins, including p53, p21, p27, NPM1, eIF4e and I- κ B.^{1,2}

Neoplasms must inactivate most major tumor suppressor pathways in order to perpetuate their phenotypes. Since the vast majority of tumor suppressor proteins and other growth modulators require nuclear localization in order to carry out their antineoplastic activities, enhancing their nuclear export leads to their functional inactivation. The control of nuclear import and export is tightly regulated by shuttle proteins in eukaryotic cells. Although there are 15 nuclear import proteins (importins) and 7 nuclear export proteins (Exportins 1-7), nearly all tumor suppressor proteins and growth regulatory proteins are exported exclusively by XPO1. All malignancies studied to date, including AML, show elevated XPO1 levels, and increasing levels often correlate with poorer prognosis.³⁻⁸ In

these malignancies, elevated XPO1 levels lead to cytoplasmic mislocalization and functional inactivation of tumor suppressor and growth regulatory proteins.

XPO1 inhibitors have been shown to block the nuclear export of key tumor suppressor proteins, leading to accumulation of these proteins in the nucleus, as nuclear import appears to proceed unimpeded. Moreover, nuclear retention appears to prevent proteasome-mediated degradation. Forced nuclear retention of various proteins can counteract a multitude of oncogenic and inflammatory pathways that perpetuate the neoplastic phenotype (Table 1).

In addition, eIF4e, which is one of the cargoes of XPO1, mediates the nuclear export of certain messenger RNAs (mRNAs) which codes for growth stimulatory proteins with short half-lives. These mRNAs include FLT3, c-KIT, and c-MYC. Therefore, XPO1 inhibition leads to nuclear retention of these mRNAs, leading to the down regulation of multiple oncogenic proteins including, further providing anti-neoplastic activity (Table 1).

Table 1. Effects of XPO1 Inhibition on Oncogenic and Inflammatory Pathways

Pathway/protein affected	Effect of XPO1 Inhibition	Reference
TP53 mutation	p73 activation, p21 activation	9
MDM2 activation	Nuclear p53 retention and activation	6
NPM1 mutation	Restoration of nuclear NPM1	10
CEBPA down-regulation	Nuclear retention and activation	9
XPO1 overexpression	XPO1 reduction	11
FLT3 activation	FLT3 reduction	9
KIT activation	KIT reduction	9
NF-KB activation	I- κ B nuclear retention and activation	8
PIK3 or AKT activation	FOXO1, -3, -4 activation	8

Karyopharm Therapeutics has recently developed novel, small molecule selective inhibitors of nuclear export (SINEs) that inhibit XPO1 by covalently binding to the Cys528 residue and thereby blocking XPO1-mediated efflux of proteins.^{6,7,9,11-13} Selinexor is an oral, first in class, slowly reversible, potent SINE that specifically blocks XPO1. Selinexor restores many of the tumor suppressor and growth regulatory proteins to the nucleus where they can carry out their normal functions. It is selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both in vitro and in vivo. All cell types exposed to selinexor in vitro undergo G1 \pm G2 cell cycle arrest, followed by a 'genomic fidelity' review. Cells with damaged genomes are induced to undergo apoptosis. Normal cells, with an intact genome, remain in transient, reversible cell cycle arrest until the export block is relieved. Selinexor and other SINE compounds are not intrinsically cytotoxic; rather, they can restore the highly effective tumor suppressing pathways that lead to selective elimination of genomically damaged (i.e., neoplastic) cells. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared.

2.1.1 Preclinical Data

A summary of the preclinical data package is included here. Please refer to the selinexor Investigator's Brochure for additional information.

Pharmacology

Selinexor has shown potent pro-apoptotic activity with a median IC₅₀ of 90 nM across a panel of 46 tumor cell lines representing a broad spectrum of tumor types. As noted above, selinexor had little effect on normal lymphocytes or other non-transformed cells, which correlated with the low incidence in animals of the typical side effects seen with most anti-cancer therapies, such as significant myelosuppression, alopecia, mucositis and other gastrointestinal dysfunction. Selinexor has shown substantial efficacy, with dosing regimens that match those currently under investigation in humans, in a variety of mouse models of solid tumors hematological malignancies and, including lung, melanoma, prostate, breast, and ovarian cancers as well as hematological malignancies including NHL, multiple myeloma and leukemia.

Pharmacokinetics and toxicology

The preclinical properties of selinexor were assessed in three species: mouse (CD1), rat (Sprague-Dawley), and monkey (cynomolgus). While PK studies were limited to male animals for all three species, toxicokinetic (TK) evaluations were conducted in both sexes for rats and monkeys as part of the selinexor toxicology studies, and no consistent sex-related differences were observed in either species. No accumulation was observed in any of the multi-dose toxicology studies with an every other day dosing regimen for selinexor. Overall, systemic exposure was generally dose-proportional in all TK studies that involved multiple dose levels. Higher maximum concentration (C_{max}) and earlier time to maximum concentration (T_{max}) values were observed in monkeys that were fasted versus fed prior to dosing. Systemic exposure (area under the curve from first to last plasma measurement, AUC_{last}) to selinexor achieved with gelatin capsules was comparable to that achieved with oral suspension dosing, with lower C_{max} and later T_{max} values observed with capsules. Results were not affected by the feeding status in monkeys. 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.

Nonclinical toxicology studies indicated that the major side effects (dose limiting toxicities, DLTs) across all species are reduced appetite with anorexia-induced weight loss partially consistent with satiety induction. High calorie foods and glucocorticoids can mitigate weight loss in animals taking SINE XPO1 inhibitors.

2.1.2 Clinical Summary

Selinexor is currently under clinical investigation for the treatment of patients with advanced hematologic and advanced solid malignancies. Three Phase 1 studies (KCP-330-001 in hematologic malignancies, KCP-330-002 in solid tumor malignancies, KCP-

330-00: food effect in sarcoma) are in progress. In addition, a Phase 1 study of selinexor in pediatric patients with AML and ALL (NCT02091245) as well as several Phase 2 studies in multiple hematologic and solid tumor indications are currently ongoing or in process of being initiated (protocol submitted to FDA). These studies and current safety and efficacy results are described in detail in the Investigator's Brochure. The first clinical trial of selinexor in an adult population was recently reported.¹⁴

As of 1 May 2014, broad anti-tumor activity has been reported during the dose-escalation phase with single agent selinexor in over 300 adult patients with heavily pretreated, relapsed/refractory, progressive solid tumor and hematologic malignancies. The most common adverse effects (AEs) have been similar to those reported in nonclinical studies and include anorexia, weight loss, nausea and fatigue. These AEs can be prevented or mitigated with dietary counselling and prophylactic supportive medications. No major organ toxicities have been observed to date, and no clinically significant cumulative toxicities have been observed in >10 months of dosing. Overall, oral selinexor pharmacokinetics was predictable, reasonably dose-proportional, and exhibited moderate to moderately high inter-patient variability across a wide dose range in male and female patients with advanced solid tumor or hematological malignancies.

Cerebellar syndrome has been seen in one adult patient who had been heavily pre-treated for recurrent pancreatic cancer. This adult patient experienced abnormal speech, loss of coordination, and was unable to walk after receiving 4 doses of selinexor at 85 mg/m² twice weekly. In this study, we have seen 2 children with similar symptoms after receiving 4 doses of selinexor at 70 mg/m² twice weekly. In both pediatric cases, the symptoms of cerebellar syndrome happened within 2 weeks of receiving selinexor. The symptoms improved after the drug was stopped.

Although data from a phase I trial of selinexor in adults with advanced solid tumors indicate that anorexia, weight loss and fatigue are common, these side effects were rarely observed in the phase one portion of this study.¹⁴ Hyponatremia was common, but was asymptomatic and easily corrected in all cases.

The phase I study in advanced hematologic malignancies (KCP-330-001) is ongoing at multiple institutions, with 168 patients enrolled as of 24 April 2014. Of the 37 patients assessed for efficacy in Arm 2 (AML) as of 28 February 2014, 5 (14%) patients had complete response, and an additional 4 patients (11%) achieved either CR(i), PR or MLFS. Thirteen patients achieved stable disease (35%) and while 15 (41%) had progressive disease (See Table 2 below).

Table 2. Best Responses in Patients with AML in KCP-330-001 as of 28 February 2014

No. of Pts. Evaluated	CR (%)	CR(i) (%)	PR (%)	MLFS (%)	SD (%)	PD (%)
37	5 (14%)	1 (3%)	2 (5%)	1 (3%)	13 (35%)	15 (41%)

Abbreviations: CR=complete response, CR(i)=complete response without hematological recovery, PR=partial response, MLFS=morphological leukemia free state, SD=stable disease, PD=progressive disease.

In the recently completed phase I portion of this study, 7 of 15 evaluable patients (47%) achieved complete response or complete response with incomplete count recovery. The complete responses observed in this study suggest activity of the combined therapeutic regimen of selinexor, fludarabine, and cytarabine. Two recent large trials evaluating regimens for refractory or first relapse of pediatric AML showed complete response rates of 48% and 64%.^{15,16} The higher risk nature of our patient population and the small number of patients in the phase I portion of this study preclude direct comparisons with the response rates reported from these studies. The characteristics of our patient cohort more closely resemble those of patients enrolled on other early phase trials for children with relapsed AML, such as a phase I trial of gemtuzumab ozogamicin and a phase II trial of clofarabine, in which response rates of 28% and 26%, respectively, were reported.^{17,18} Notably, two patients in the present study became MRD negative after receiving only selinexor, indicating that there is a patient population who might benefit from single-agent selinexor therapy. In addition, three of the seven patients who attained CR or CRi were in second relapse, suggesting that this therapy may be beneficial for patients at more advanced stage of relapse.

In summary, early results from ongoing studies demonstrated tolerability and responses across a variety of hematologic malignancies.¹⁹ Constitutional symptoms of weight loss, fatigue, and anorexia were common in adults but can be successfully prevented or mitigated using aggressive prophylactic supportive measures.

Potential Risks

The most common side effects ($\geq 20\%$) are nausea, loss of appetite, fatigue, vomiting, weight loss, thrombocytopenia and anemia. Asymptomatic hyponatremia (median sodium nadir, 128.5 meq/L, range 123-132 meq/L), was common in the phase I portion of this study, but was easily corrected by oral or intravenous supplementation in all cases.

Less common side effects ($<20\%$) are diarrhea, change in taste, dizziness, dehydration, constipation, dry mouth, changes in vision including blurred vision (without objective findings on ophthalmological exam), decrease in neutrophils, decrease in white blood cells, and low sodium.

Side effects that are rarely ($< 5\%$) observed include: worsening of pre-existing cataracts, infection, sepsis – a potentially life-threatening complication of infection and pneumonia.

Cerebellar syndrome has been seen in one adult patient who had been heavily pre-treated for recurrent pancreatic cancer. This adult patient experienced abnormal speech, loss of coordination, and was unable to walk after receiving 4 doses of selinexor at 85 mg/m² twice weekly. In this study, we have seen 2 children with similar symptoms after receiving 4 doses of selinexor at 70 mg/m² twice weekly. In both pediatric cases, the symptoms of cerebellar syndrome happened within 2 weeks of receiving selinexor. The symptoms improved after the drug was stopped.

2.1.3 Reproductive Risks

Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important patients understand the need to use birth control while on this study. Female patients of child-bearing potential who are sexually active must agree to use dual methods of contraception and have a negative serum pregnancy test at screening (≤ 3 days prior to first dose), and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients who are sexually active, effective methods of contraception must be used throughout the study and for three months following the last dose.

2.2 Rationale for this Study

The present proposal is a pilot study of selinexor in combination with fludarabine and cytarabine in pediatric patients with refractory or relapsed hematologic malignancies. The starting dose will be 30 mg/m²/dose, which is well below the maximum adult Phase I dose of 70 mg/m² (trial KCP-330-001) and 2 dose levels below the adult Phase II AML dose of 55 mg/m² (trial KCP-330-008). The chemotherapy backbone will be fludarabine/cytarabine, an active combination that has been used to treat patients with relapsed AML for over 20 years (given alone, with G-CSF in the FLAG regimen, or with idarubicin in the ida-FLAG regimen). In addition, these agents are also active in ALL.

We found that six doses of selinexor, given at 55 mg/m²/dose, are well tolerated in combination with fludarabine and cytarabine in children with relapsed and refractory acute leukemia. The dose-limiting reversible cerebellar toxicity was only observed at a dose level of 70 mg/m². Complete responses observed in this high risk population, after single agent and combination therapy, suggests that selinexor may have a role in the treatment of pediatric acute leukemia. Taken together, this phase I study of selinexor, along with promising preclinical studies demonstrating efficacy in high-risk leukemia and on leukemia-initiating cells, justify further studies to evaluate the safety and efficacy of selinexor-based therapy in children with relapsed and refractory acute leukemia. Based upon PK/PD data from the phase 1 portion of the study, along with PK/PD and selected phase II data from unpublished adult trials, we have chosen to proceed with phase II dose of 40 mg/m²/dose.

3.0 ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

3.1 Inclusion Criteria

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

- 3.1.1 **Phase I (completed)**: Participants must have a diagnosis of AML, MDS, ALL or MPAL and must have disease that has relapsed or is refractory to chemotherapy, or that has relapsed after hematopoietic stem cell transplantation (HSCT)
- a) Refractory disease is defined as persistent disease after at least two courses of induction chemotherapy.
 - b) Patients with AML, MPAL or MDS are eligible at first or subsequent relapse, whereas patients with ALL are eligible at second or subsequent relapse or any relapse that is refractory to salvage chemotherapy.
 - c) Patients with AML or ALL must have $\geq 5\%$ leukemic blasts in the bone marrow or increasing levels of MRD in the bone marrow as assessed by flow cytometry. If an adequate bone marrow sample cannot be obtained, patients may be enrolled if there is unequivocal evidence of leukemia in the peripheral blood.
- 3.1.2 **Phase II**: Participants must have a diagnosis of AML and must have disease that has relapsed or is refractory to chemotherapy, or that has relapsed after hematopoietic stem cell transplantation (HSCT)
- Refractory disease is defined as persistent disease after at least two courses of induction chemotherapy.
 - Patients are eligible at first or subsequent relapse or any relapse that is refractory to salvage chemotherapy.
- 3.1.3 Patients must have $\geq 5\%$ leukemic blasts in the bone marrow and/or increasing levels of MRD in the bone marrow as assessed by flow cytometry. If an adequate bone marrow sample cannot be obtained, patients may be enrolled if there is unequivocal evidence of leukemia in the peripheral blood.
- 3.1.4 Adequate organ function defined as the following:
- Direct bilirubin ≤ 1.5 x institutional upper limit of normal (IULN)
 - AST (SGOT)/ALT (SGPT) < 3 x IULN
 - Creatinine within normal institutional limits for age
- 3.1.5 Prothrombin time (PT) and partial thromboplastin (PTT) ≤ 1.5 x IULN.
- 3.1.6 Age criteria: Patients treated at collaborating sites and current St. Jude patients who are on therapy or within 3 years of completion of therapy must be ≤ 24 years old. All other St. Jude patients must be ≤ 21 years old.
- 3.1.7 Patients must be able to swallow tablets.
- 3.1.8 Performance status: Lansky ≥ 50 for patients who are ≤ 16 years old and Karnofsky $\geq 50\%$ for patients who are > 16 years old.

3.1.9 Patients must have fully recovered from the acute effects of all prior therapy. For patients who have received prior HSCT, there can be no evidence of GVHD and greater than 60 days must have elapsed since the HSCT.

3.2 Exclusion Criteria

3.2.1 History of cerebellar toxicity or cerebellar neurological findings on exam.

3.2.2 Must not be pregnant or breastfeeding. Female patients who are sexually active and of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients who are sexually active, effective methods of contraception must be used throughout the study and for three months following the last dose. Abstinence is an acceptable form of contraception.

3.2.3 Patients with Down syndrome, acute promyelocytic leukemia, juvenile myelomonocytic leukemia, Fanconi anemia, Kostmann syndrome, Shwachman syndrome, or other bone marrow failure syndromes are not eligible.

3.2.4 Use of investigational agents, with the exception of gemtuzumab ozogamicin, within 30 days.

3.2.5 Any significant concurrent disease, illness, or psychiatric disorder that would compromise patient safety or compliance, study participation, follow up, or interpretation of study research.

3.2.6 Unstable cardiovascular function:

- symptomatic ischemia
- congestive heart failure NYHA Class > 3
- myocardial infarction (MI) within 3 months

3.2.7 Uncontrolled infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose. Infections controlled on concurrent anti-microbial agents are acceptable, and anti-microbial prophylaxis per institutional guidelines are acceptable.

3.2.8 *Known* human immunodeficiency virus (HIV) infection (pre-study testing not required).

3.2.9 Patients with malabsorption syndrome, or any other disease significantly affecting gastrointestinal function.

3.2.10 Prior treatment with selinexor.

3.3 Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the ‘Participant Eligibility Checklist.’ The study team will enter the eligibility checklist information into the Patient Protocol Manager (PPM) system. Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The complete signed consent/assent form(s) must be faxed or emailed to the CPDMO at [REDACTED] to complete the enrollment process. The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member is on call Saturday, Sunday, and holidays from 8:00 am to 5:00 pm. Enrollments may be requested during weekends or holidays by calling the CPDMO “On Call” cell phone [REDACTED] or referencing the “On Call Schedule” on the intranet.

3.4 Enrollment on Study at Collaborating Sites

Collaborating Site research participants should be registered at St. Jude within 24 hours of enrollment at the site. The completed Eligibility Checklist and entire signed Informed Consent should be faxed to [REDACTED]. Please call [REDACTED] if confirmation of the enrollment information is needed. The Protocol Eligibility Coordinator will then register the research participant in the Patient Protocol Manager (PPM) system.

4.0 TREATMENT PLAN

4.1 Overview

Patients must have fully recovered from the acute effects of all prior therapy before starting selinexor. In addition, at least 14 days must have elapsed since the completion of myelosuppressive therapy or gemtuzumab ozogamicin and the first dose of selinexor. At least 24 hours must have elapsed since the completion of low-dose or non-myelosuppressive therapy, such as hydroxyurea, vincristine, steroids, or low-dose cytarabine (up to 100 mg/m²/day), and the first dose of selinexor. For patients who have received prior HSCT, there can be no evidence of GVHD and greater than 60 days must have elapsed since the HSCT.

This study will include two phases. The dose-escalation phase will characterize the dose-limiting toxicities (DLTs) and determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of selinexor when given in combination with fludarabine and cytarabine. The RP2D will be chosen based on the MTD and totality of the data (clinical, PK, and PD data from this and other trials). The phase II cohort will further assess the safety and will explore the efficacy of this combination.

Selinexor will be given orally on days 1, 3, 8, 10, 22 and 24 of each cycle.

Fludarabine (30 mg/m²/dose IV over 30 minutes daily) and **cytarabine** (2 gram/m²/dose IV over 4 hours daily) will be given on days 16 (\pm 2 days) through 20 (\pm 2 days). Chemotherapy may be delayed if clinically indicated.

For patients who achieve CR or CRi with negative MRD or with MRD that has decreased at Day 15, the treating physician may continue single agent selinexor without fludarabine and cytarabine. In this case, selinexor should be given on days 1, 3, 8, 10, 15, 17, 22 and 24.

Patients who achieve CR or CRi status (as defined in Section 8.1) at day 15 (regardless of MRD status) may proceed directly to HSCT at the discretion of the treating physician.

Fludarabine and cytarabine may be given before Day 16 if the treating physician, after consulting with the principal investigator (PI), believes it is in the patient's best interest based on disease progression. In general, the fludarabine/cytarabine combination should begin prior to day 16 if the leukocyte count is greater than 50,000/ μ l and increases by >50%. For example, if the leukocyte count is 30,000/ μ l and increases to 46,000/ μ l, fludarabine and cytarabine will start on day 16 as planned. However, if the leukocyte count is 60,000/ μ l and increases to 91,000/ μ l, fludarabine and cytarabine may be started early.

Note that these are guidelines that should be used in the context of each patient's clinical condition.

If fludarabine and cytarabine are given prior to Day 16, the administration of selinexor should be held at start of fludarabine and cytarabine administration and resumed 3 days after completion of fludarabine and cytarabine to complete total of three weeks of selinexor during course one.

Diagnostic lumbar puncture and **intrathecal (IT) chemotherapy** should be given prior to cycle 1, but may be delayed if clinically indicated. IT cytarabine, IT methotrexate, and IT methotrexate/ hydrocortisone/cytarabine (MHA) are all acceptable. Note that the first dose of IT chemotherapy may be given prior to or after enrollment on SELHEM.

Patients without evidence of central nervous system (CNS) leukemia will receive no further IT therapy during cycle 1. Patients with CNS disease (defined as the presence of any blasts in the CSF) will receive weekly ITMHA until the cerebrospinal fluid becomes free of leukemia.

For patients who require IT therapy on day 15, administration of IT therapy should be separated from administration of IV fludarabine and cytarabine by at least one day.

4.2 Intrathecal Chemotherapy

Patient Age	Methotrexate	Hydrocortisone	Cytarabine	Volume
< 1 year	6 mg	12 mg	18 mg	6 ml
1-2 years	8 mg	16 mg	24 mg	8 ml
2-3 years	10 mg	20 mg	30 mg	10 ml
> 3 years	12 mg	24 mg	36 mg	12 ml

Leucovorin rescue (5 mg/m²/dose, max 5 mg) PO will be given at 24 and 30 hours after each triple intrathecal treatment. Follow plasma methotrexate levels (starting 24 hours after intrathecal therapy and until level becomes undetectable) in patients with renal dysfunction or extra fluid in third space, and rescue with leucovorin as clinically indicated.

4.3 Dose-Escalation Cohort (*completed*)

As described above, the starting dose of selinexor will be 30 mg/m²/dose, which is well below the current adult Phase I dose (trial KCP-330-001) of 70 mg/m² which has cleared DLT and below the adult Phase II dose of 55 mg/m² (trial KCP-330-008).

Selinexor, initially at 30 mg/m²/dose, will be given twice weekly (on days 1 and 3) and escalated or de-escalated based on tolerability (Dose level -1, 1, 2, and 4 are shown in Table 3 below). The rolling-6 design will be used for the conduct of this study.

A full safety evaluation will be conducted when participants have completed 28 days of therapy. Only cycle 1 of therapy will be used to evaluate the DLT.

Two to 6 participants can be concurrently enrolled onto a dose level, dependent on:

- 1) the number of participants enrolled at the current dose level, and
- 2) the number of participants who have experienced DLT at the current dose level, and
- 3) the number of participants entered but with tolerability data pending at the current dose level.

Accrual is suspended when a cohort of 6 has enrolled or when the study endpoints have been met.

The decision as to which dose level to enroll a participant is based on the number of participants currently enrolled and evaluable, the number of participants experiencing DLT, and the number of participants still at risk of developing a DLT at the time of new participant entry. For example, when 3 participants are enrolled onto a dose level, if toxicity data is available for all 3 participants and no DLTs are observed when the 4th participants enter, the dose is escalated and the 4th participants is enrolled to the next higher dose level; if toxicity data is not yet available for 1 or more of the three participants and no DLT has been observed, or if 1 DLT has been observed, the new participant is entered at the same dose level; if 2 or more DLTs have been observed from the 3 participants, the dose level is de-escalated. This process is repeated for the 5th and 6th participants.

Table 3. Dose-escalation plan

Dose level	Selinexor (mg/m ² /dose on days 1, 3, 8, 10, 22 and 24)	Fludarabine (mg/m ² /dose on days 16-20)	Cytarabine (g/m ² /dose on days 16-20)
-1	20	30	2
1	30	30	2
2	40	30	2
3	55	30	2
4	70	30	2

4.4 Phase II Cohort

The Phase II portion of the study will enroll patients at a **selinexor dose of 40 mg/m²/dose** on the same administration schedule as the dose escalation cohort.

Evaluation of response to single agent selinexor: unless there is evidence of progressive disease by examination of the blood, participants should undergo bone marrow evaluation on day 15 (\pm 2 days). This evaluation must be performed prior to administration of fludarabine and cytarabine.

Evaluation of response to Cycle 1: participants should undergo response evaluation between days 42 and 56 of Cycle 1 (with the exception of any patient who obtains complete response at Day15 and elects to continue single agent selinexor and forego fludarabine and cytarabine therapy). Patients may be evaluated earlier if there is evidence of hematopoietic recovery or at discretion of treating physician. In cases with hypocellular marrows (<10% cellularity), repeat bone marrow examinations should be considered when there is evidence of hematopoietic recovery.

Table 4. Treatment administration

Drug	Dose	Route	Schedule
Selinexor	40 mg/m ²	PO	Days 1, 3, 8, 10, 22 and 24
Fludarabine	30 mg/m ² /dose	IV over 30 minutes	Days 16-20 ^a
Cytarabine	2 gram/m ² /dose	IV over 4 hours ^b	Days 16-20 ^a

^a *May be given earlier or later, as clinically indicated*

^b *Cytarabine should start at least 3.5 hours after completion of fludarabine*

Selinexor should be administered with food or within 30 minutes after a meal. The dose will be determined according to Appendix I and rounded to the nearest 10 mg.

4.5 Response Evaluations

Bone Marrow Evaluation of single agent selinexor during Cycle 1: unless there is evidence of progressive disease by examination of the blood, participants should undergo bone marrow evaluation on day 15 (\pm 2 days). This evaluation must be performed prior to administration of day 15 therapy.

Evaluation of response to Cycle 1: participants should undergo response evaluation between days 42 and 56 of Cycle 1 (with the exception of patients who obtain complete response at Day 15 and elect to continue single agent selinexor and forego fludarabine and cytarabine therapy). Patients may be evaluated earlier if there is evidence of hematopoietic recovery or at discretion of treating physician. In cases with hypocellular marrows (<10% cellularity), repeat bone marrow examinations should be considered when there is evidence of hematopoietic recovery.

4.6 Definitions of Dose-Limiting Toxicities (DLT)

Toxicities will be graded according to the CTCAE Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. DLT is based on non-hematologic toxicities that occur during Cycle 1 and that are deemed to be possibly attributable to selinexor.

4.6.2.1 Non-hematologic DLT (*phase I only*)

- Any Grade 5 event
- Any Grade 4 event that is at least possibly related to selinexor, unless event is clearly and incontrovertibly due to extraneous causes or disease progression

4.6.2.2 Hematologic toxicity (*phase I only*)

Grade 3 or 4 hematologic toxicities will be monitored, but will not be considered dose-limiting toxicities.

4.6.2.3 Dose modifications (See Appendix IV)

During Cycle 1 patients should receive 5 of the 6 intended doses of selinexor; failure to receive 5 doses by Day 35 because of toxicity will be considered a DLT (*phase I only*).

Note that at least 48 hours must pass between doses. Doses should be delayed, rather than omitted, for the following non-hematologic toxicities. Patients should also be treated aggressively with supportive care to reduce toxicities.

Weight loss: if a participant develops Grade 3 weight loss, the next dose of selinexor should be delayed until the weight loss resolves to Grade ≤ 2 . If weight loss does not improve to Grade ≤ 2 within 7 days, this participant will have experienced a DLT (*phase I only*).

Electrolyte abnormalities: if a participant develops Grade ≥ 3 uncorrectable electrolyte abnormalities, the next dose of selinexor should be delayed until the abnormalities resolve to Grade ≤ 2 . If abnormalities do not improve to Grade ≤ 2 within 7 days despite attempts to correct, this participant will have experienced a DLT (*phase I only*).

Infection: the occurrence of Grade 4 infection will not be considered a DLT (*phase I only*). Selinexor should be delayed in any participant with Grade 4 infection or clinical sepsis until condition has clinically stabilized. If during Cycle 1, selinexor is suspended

due to Grade 4 infection or clinical sepsis and participant misses ≥ 3 doses of study drug, the participant will be deemed not evaluable and removed from study. These patients will be replaced during the DLT period, but will be included in the evaluation of the safety profile of the regimen and determining the recommended phase 2 dose (*phase I only*). Selinexor dosing (at the same dose level) can be re-initiated once the patient's condition has stabilized clinically, even when the patient is taking antimicrobial or other agents.

Other DLTs: in the event of a DLT in Cycle 1 (*phase I only*), or other toxicity that warrants discontinuation in the opinion of the investigator, selinexor should be discontinued and the participant removed from study.

The following adverse events will not be considered DLTs (*phase I only*):

- Grade 3 nausea, vomiting or diarrhea (unless persisting > 3 days with appropriate treatment of anti-emetics or anti-diarrheals)
- Alopecia of any grade
- Weight loss of less than 20%
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions

4.7 Cycle 2 and Subsequent Courses

Participants who have acceptable toxicity (Grade 3 non-hematologic toxicity that has resolved, or stable Grade 1-2 non-hematologic toxicity) and have PR or better response are eligible to receive a second course of therapy. Intrathecal therapy may be given prior to Cycle 2 at the discretion of the treating physician.

4.7.1 Cycle 2 combination therapy

Participants may begin Cycle 2 combination therapy when the absolute neutrophil count (ANC) is $\geq 300/\mu\text{l}$ and rising and the platelet count $\geq 30,000/\mu\text{l}$ and rising.

- Selinexor (40 mg/m²/dose) will be given orally on days 1, 3, 8, 10, 22 and 24 at the same dose that was given in Cycle 1.
- Fludarabine (30 mg/m²/dose IV over 30 minutes daily) on days 15-19
- Cytarabine (2 gram/m²/dose IV over 4 hours daily) will be given on days 15-19

Combination therapy will be limited to a maximum of 2 cycles.

4.7.2 Cycle 2 selinexor single agent therapy

Patients who had at least partial response on Day 15 of Cycle 1 may receive selinexor alone during Cycle 2 after consultation with the Principal Investigator. Participants may begin Cycle 2 (and subsequent) single agent therapy when the absolute neutrophil count (ANC) is $\geq 500/\mu\text{l}$ and rising and the platelet count $\geq 50,000/\mu\text{l}$ and rising.

Patients may continue to receive single agent selinexor as long as there is clinical benefit and no disease progression or unacceptable toxicities.

For patients who achieve complete remission, protocol therapy will be discontinued when a suitable donor has been identified and the patient is ready to proceed to HSCT, or two cycles beyond achieving remission. In general, therapy with selinexor should be discontinued approximately 2 weeks prior to HSCT.

4.8 Supportive Care and Concomitant Therapy

Anorexia and weight loss: Selinexor frequently causes anorexia and weight loss. Thus, participants should be weighed daily while inpatient and at every outpatient visit. High caloric supplements and appetite stimulating agents should be considered in all participants.

Prophylactic treatment to prevent anorexia and nausea during is strongly recommended. An example regimen is outlined below, but exact regimen is at the discretion of the treating institution or physician.

- Ondansetron 0.15 mg/kg/dose TID, starting prior to the first dose of selinexor and continuing for at least 24 hours after the dose (may be continued throughout therapy as needed). Granisetron or other appropriate 5-HT₃ antagonist may be substituted for ondansetron.
- Dexamethasone 5 mg/m²/day x 3 days (given on the day prior to, the day of, and the day after selinexor).
- Olanzapine 1.25 to 2.5 mg daily (may be divided BID), starting one day prior to selinexor. If olanzapine is tolerated, the dose may be increased to 5 mg daily as needed.

Missed doses: a maximum of two doses may be given per week. If the dose was missed for more than 24 hours, the dose will be skipped and the next dose will be taken as per schedule. If the dose was missed within 24 hrs, then it will be replaced. Doses should not be administered in less than 48 hours apart and all missed doses should be documented.

Vomited doses: if a dose is vomited within one hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will still be considered a complete dose. If a patient missed a full week of dosing for non-study drug related events (e.g., a required medical procedure or an unanticipated personal emergency), the days missed will not be replaced.

Compliance to study medication: will be recorded by study personnel after discussion with the patient and drug accountability. Compliance to study medication will be done by the investigator or delegate and recorded in source documents. The date will be recorded as per study drug schedule. The principal investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the CRF and drug accountability logs for verification

with the reasons. The investigator/designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients

Antineoplastic therapy: Concurrent cancer therapy, including chemotherapy (other than protocol drugs fludarabine, cytarabine and ITHMA), immunotherapy, or biologic therapy cannot be administered to patients while receiving selinexor.

Radiation therapy: Concurrent radiotherapy is prohibited.

Investigational agents: No other investigational agents may be given while the patient is on protocol therapy.

Growth factors: The routine use of filgrastim (G-CSF, Neupogen®) or other growth factors is discouraged, but may be used in cases of documented infection or sepsis during periods of neutropenia, according to institutional practice.

Conjunctivitis prophylaxis: Dexamethasone or prednisolone ophthalmic solution or artificial tears (e.g., hydroxymethylcellulose, hypromellose, polyvinyl alcohol), 2 drops in each eye every 4 hours while awake, should be used during cytarabine administration and for 24 hours after completion to prevent conjunctival irritation.

Drugs undergoing glutathione conjugation: The primary metabolism of selinexor is inactivation by glucuronidation; conjugation with glutathione is a secondary mode of metabolism. Because acetaminophen is associated with glutathione depletion, patients should not take acetaminophen on days of selinexor administration.

Prophylaxis and treatment of metabolic derangement: Care should be taken to prevent hyperuricemia and hyperphosphatemia in participants with large tumor burdens. Such participants should receive IV hydration at 1500-3000 mL/m²/day before the initiation of therapy, oral phosphate binders, and recombinant urate oxidase or allopurinol as needed.

Prophylaxis for *Pneumocystis jiroveci* pneumonia: All participants should receive prophylaxis for *Pneumocystis jiroveci* pneumonia according to institutional guidelines.

Prophylaxis for fungal infections: Because patients with relapsed leukemia are at high risk for fungal infections, all participants should receive antifungal prophylaxis according to institutional guidelines. Prophylaxis with voriconazole or posaconazole are strongly recommended.

Prophylaxis for bacterial infections: Because patients with relapsed leukemia are also at high risk for bacterial infections, all participants should receive antibiotic prophylaxis according to institutional guidelines. We recommend starting prophylactic antibiotics when the ANC \leq 1000 and falling or predicted to fall and continued until the ANC \geq 100 and rising.

Management of febrile neutropenia: All patients with fever $\geq 38.3^{\circ}\text{C}$ on a single occasion or $\geq 38^{\circ}\text{C}$ on two occasions within 12 hours should be hospitalized and treated immediately with broad spectrum antibiotics according to institutional guidelines.

Prophylactic antiemetic: treatment is recommended prior to the first dose of selinexor, although selinexor does not usually cause high grade nausea or vomiting. 5-HT₃ receptor antagonists, with or without glucocorticoids, appear to be effective at preventing nausea associated with selinexor. Olanzapine or mirtazapine are also effective at reducing nausea. Neurokinin-1 receptor antagonists (e.g., aprepitant) should be considered in case of uncontrolled emesis with standard treatments as described above. Neurokinin-1 receptor antagonists can be given with dexamethasone and 5-HT₃ receptor antagonists. Metoclopramide hydrochloride given prior to meals and dronabinol may be used as well.

Selinexor is infrequently associated with delayed, resistant emesis. Many of the regimens associated with delayed emesis are classified as high-emetic risk, and 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 glucocorticoids 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. In adult studies, olanzapine once daily (typically given at night to mitigate sedative effects) was proven 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 is typically used in children greater than 10 years of age.

Restrictions and precautions:

- Alcohol: Ethanol should be avoided on selinexor dosing days as it may compete for glutathione mediated metabolism.
- Fasting: Patients on selinexor should maintain an adequate diet.
- Medications: Acetaminophen (paracetamol, Tylenol[®]) and products containing acetaminophen should be avoided on days of selinexor administration as it may compete with glutathione mediated metabolism.
- Diet: There are no dietary restrictions on this study. Patients should maintain adequate caloric and fluid intake.

5.0 DRUG INFORMATION

5.1 SELINEXOR (KPT-330)

Description: Selinexor is a selective inhibitor of nuclear export (SINE). Selinexor specifically blocks XPO1-mediated nuclear export by forming a slowly reversible covalent bond with the nuclear export protein XPO1.

Selinexor is manufactured by KABS Laboratories (Montreal, ON) for Karyopharm, Therapeutics (Newton, MA) using methods in accordance with Food and Drug Administration (FDA) guidelines for the manufacture and testing of antineoplastic agents for human use. Selinexor is an investigational agent supplied to investigators by Karyopharm Therapeutics.

Selinexor will be supplied as clear-coated tablets for oral use in two (2) dose strengths: 10 and 25 mg of active ingredient per tablet. Bulk bottles of 50 tablets per bottle will be supplied for each of the two strengths. Tablets of selinexor should not be crushed because of increased risk of dermatologic toxicity if powder comes in contact with skin. Selinexor will be available in 20 mg strength tablets, provided in blister packs, as an additional option for patients in the future.

Storage and stability: Tablets of selinexor drug product will be stored at ambient temperature in white HDPE bottles, in a locked and secured area with restricted access. Selinexor tablets can be stored long term between 5 and 30 °C, but should not be stored frozen or at freezer temperatures. Room temperature storage is recommended.

Stability of tablets: Selinexor tablets are currently in on-going stability studies. The current expiry is 30 months for the 10 mg and 25 mg bottled samples and 21 months for the blister-packed 20 mg tablets, and will be extended when further stability data becomes available.

Handling: Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Supplier: Selinexor is an investigational agent and will be supplied free-of-charge from Karyopharm Therapeutics, Inc.

Administration: Selinexor tablets for oral administration should be taken within 30-minutes of food consumption.

Each dose will consist of selinexor for oral administration based on mg/m² basis, and should be based on the patient's actual body surface area (BSA) calculated at baseline (Cycle 1) and at the start of each subsequent cycle. See Appendix I for Dosing Guidelines

Toxicity: Please see Investigator's brochure and safety updates for full information.

Ordering: Karyopharm Therapeutics will supply the drug in the form of 10 mg and 25 mg coated tablets in 50 count bottles and 20 mg blister packed tablets. Drug order forms with all the needed contact information will be provided at the start of the trial, along with recommended initial and resupply stock orders. Orders submitted via e-mail will be filled within 5 business days of receipt.

Accountability: The investigator, or a responsible party designated by the investigator at each site, must maintain a careful record of the inventory and disposition of the agent

(investigational or free of charge) using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the CTEP website at <http://ctep.cancer.gov/protocolDevelopment> for the “Policy and Guidelines for Accountability and Storage of Investigational Agents” or to obtain a copy of the drug accountability form).

Destruction and return: At the end of the study, unused supplies of selinexor should be destroyed according to institutional policies at the request of Karyopharm Therapeutics. Destruction will be documented in the DARF.

5.2 Fludarabine (Fludara[®], fludarabine phosphate, 2-fluoro-ara-AMP)

Source and pharmacology: Fludarabine phosphate is a synthetic purine nucleoside analog. It acts by inhibiting DNA polymerase, ribonucleotide reductase and DNA primase by competing with the physiologic substrate, deoxyadenosine triphosphate, resulting in inhibition of DNA synthesis. In addition, fludarabine can be incorporated into growing DNA chains as a false base, thus interfering with chain elongation and halting DNA synthesis. Fludarabine is rapidly dephosphorylated in the blood and transported intracellularly via a carrier mediated process. It is then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate form. Approximately 23% of the dose is excreted as the active metabolite in the urine (with dosages of 18-25 mg/m²/day for 5 days). Renal clearance appears to become more important at higher doses, with approximately 41-60% of the dose being excreted as the active metabolite in the urine with dosages of 80-260mg/m².

Formulation and stability: Fludarabine is supplied in single-dose vials containing 50 mg fludarabine as a white lyophilized powder and 50 mg of mannitol. The intact vials should be stored under refrigeration. Each vial can be reconstituted by adding 2 ml of sterile water for injection resulting in a final concentration of 25 mg/ml. Because the reconstituted solution contains no antimicrobial preservative, the manufacturer recommends that it should be used within 8 hours of preparation. The solution should be further diluted in 5% dextrose or 0.9% NaCl prior to administration.

Supplier: Commercially available.

Toxicity: The major dose-limiting toxicity of fludarabine is myelosuppression. Nausea and vomiting are usually mild. Side effects reported commonly include, anorexia, fever and chills, alopecia and rash. Neurotoxicity can be manifested by somnolence, fatigue, peripheral neuropathy, mental status changes, cortical blindness and coma and is more common at high doses. Neurotoxicity is usually delayed, occurring 21-60 days after the completion of a course of therapy and may be irreversible. Side effects reported less commonly include diarrhea, stomatitis, increased liver function tests, liver failure, chest pain, arrhythmias and seizures. Pulmonary toxicity includes allergic pneumonitis characterized by cough, dyspnea, hypoxia and pulmonary infiltrates. Drug induced pneumonitis is a delayed effect, occurring 3-28 days after the administration of the third or later course of therapy. Administration of corticosteroids usually results in resolution of these symptoms.

Guidelines for administration: IV infusion over 30 minutes. See treatment plan section.

5.3 Cytarabine (Cytosine arabinoside, Ara-C, Cytosar[®])

Source and pharmacology: Cytarabine is a deoxycytidine analogue. It must be tri-phosphorylated to its active form, ARA-CTP, by deoxycytidine kinase and other nucleotide kinases. Ara-CTP inhibits DNA polymerase. In addition, ara-CTP is incorporated into DNA as a false base, causing inhibition of DNA synthesis. It is cell cycle, S phase specific. Cytarabine does not penetrate the blood brain barrier. It is converted to its inactive form, uracil arabinoside, by pyrimidine nucleoside deaminase. Approximately 80% of the dose is recovered in the urine, mostly as uracil arabinoside (ara-U).

Formulation and stability: Cytarabine is available in multi-dose vials containing 100, 500, 1000 and 2000mg of lyophilized drug. Intact vials can be stored at room temperature. **For IV use**, either sterile water for injection or bacteriostatic water for injection can be used to reconstitute the lyophilized drug. **For intrathecal use**, only sterile water for injection should be used for reconstitution. The 100 and 500 mg vials are reconstituted with 2 and 10 ml respectively resulting in a final concentration of 50 mg/ml. The 1000 and 2000 mg vials are reconstituted with 20 ml and 40 ml respectively resulting in a final concentration of 50 mg/ml. After reconstitution, the drug is stable for 8 days at room temperature.

Supplier: Commercially available.

Toxicity: Myelosuppression is the dose limiting adverse effect, with leukopenia and thrombocytopenia being predominant. Other adverse effects reported commonly include nausea and vomiting (may be severe at high doses), diarrhea, mucositis, anorexia, alopecia, skin rash and liver dysfunction. A flu-like syndrome characterized by fever, muscle and bone aches is common. Less common side effects include allergic reactions and cellulitis at the injection site. High doses of cytarabine can cause conjunctivitis, hepatitis, and a group of CNS symptoms including somnolence, peripheral neuropathy, ataxia, and personality changes. CNS symptoms are usually reversible and are more common in patients who have received previous cranial irradiation. In addition, a syndrome of sudden respiratory distress progressing to pulmonary edema has occurred.

Guidelines for administration: Intrathecal and intravenous. See treatment plan section of protocol.

5.4 Intrathecal Triples (ITMHA, methotrexate/hydrocortisone/cytarabine)

Source and pharmacology: The intrathecal route of administration of a drug produces more consistent CSF drug concentrations at relatively smaller doses because of the volume difference between the CSF and blood compartments (140 mL vs. 3500 mL in an adult). (The CSF volume of children after the first 3 years is equivalent to that of an adult). Drug half-lives are longer as well because clearance is related to flow rather than metabolism or protein binding. Intrathecal methotrexate has a biphasic elimination curve from the CSF with a $t_{1/2}$ of 4.5 and 14 hours respectively. Following IT injection of

cytarabine the elimination of the drug from the CSF is biphasic with a $t_{1/2}$ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

Formulation and stability: Methotrexate 25 mg/mL preservative free 2 mL vial or methotrexate 20 mg preservative free sterile powder for injection vial. Cytarabine 100 mg preservative free sterile powder for injection. Hydrocortisone sodium succinate 100 mg vial sterile powder for injection.

Toxicity: Nausea, vomiting, fever, headache.

Guidelines for administration: See treatment plan, Section 4.2.

6.0 REQUIRED EVALUATIONS, TESTS, OBSERVATIONS

6.1 Pre-Treatment Clinical Evaluations

- Complete medical history
- Physical exam with vital signs
- Height, weight, BSA
- Complete blood count with differential*
- Chemistry profile: glucose, electrolytes, BUN, creatinine, LDH, uric acid, bilirubin, SGOT, SGPT, calcium, phosphorous, magnesium, total protein and albumin*
- Coagulation screen*
- HLA typing, if not done previously
- Chest x-ray*
- EKG, echocardiogram*
- Lumbar puncture with CSF cell count and cytology.
- Ophthalmic exam (preferably prior to first dose of selinexor, but may be obtained within one week of dose #1).
- Serum pregnancy test of females of childbearing potential
- Bone marrow evaluation for morphology, immunophenotyping, cytogenetics, molecular diagnosis, minimal residual disease (MRD), and tissue banking*. Morphologic examination and MRD are required for all patients. Immunophenotyping, cytogenetic analysis, and molecular analysis should be performed as clinically indicated (e.g., if not done at the time of relapse). For patients with elevated leukocyte counts and high blast percentages, and patients too ill to undergo bone marrow aspirate, all diagnostic studies may be performed on blood rather than bone marrow. MRD studies must be performed centrally at St. Jude, whereas other diagnostic studies may be performed locally as desired by the treating physician.

** Complete blood count and chemistry profile should be performed within 48 hours of first dose of selinexor. Chest x-ray, EKG, and echocardiogram should be performed within 2 weeks of first dose of selinexor. Tissue banking applies to participants who have signed St. Jude TBANK consent only. TBANK is an optional protocol for collaborating sites.*

6.2 Evaluations During Therapy

	During Cycle 1-2 (combination therapy)	Cycles 2-5 selinexor single agent
Clinical studies		
Physical exam, BSA, vital signs, performance status	Weekly	Prior to each cycle and then every 2 weeks
CBC with diff	Weekly and as clinically indicated	Prior to each cycle and then every 2 weeks
Serum chemistries ¹	Weekly, and as clinically indicated	Prior to each cycle and then every 2 weeks
Ophthalmic examination ²	Prior to cycle ²	As clinically indicated
Bone marrow aspirate and/or biopsy for morphology, MRD	Prior to Cycle 1 and 2	Every other cycle
Bone marrow aspiration for MRD and correlative biological studies – see Section 7.3 and Appendix V	Prior to Cycle 1, at day 15, and at the end of Cycle 1	---
EKG and echocardiogram	Prior to each cycle	Prior to each cycle
Correlative research studies		
Pharmacokinetics – see Section 7.1	Cycle 1, dose escalation cohort (phase I) only	---
Pharmacodynamics (XPO1 expression levels and cytokine analysis) – see Sections 7.2.1 and 7.2.2	Cycle 1, dose escalation cohort (phase I) only	---

¹Serum chemistries include: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, uric acid, ALT, AST, alkaline phosphatase, total bilirubin and LDH
²Full ophthalmic examination will be conducted on all patients by an ophthalmologist or optometrist at screening and as clinically indicated during thereafter. Ideally, the initial exam should be conducted prior to the first dose of selinexor, but may be conducted within one week of the first dose.

6.3 Response Evaluations

6.3.1 Evaluation of response to Cycle 1 combination therapy

All participants should undergo response evaluation between days 42 and 56 of Cycle 1. In addition to bone marrow aspiration, bone marrow biopsy should be considered to evaluate cellularity. In cases with hypocellular marrows (<10 % cellularity), repeat bone marrow examination should be considered when there is evidence of hematopoietic recovery. If multiple bone marrow examinations are performed after a course of therapy, the last examination will be used to classify the response to that course.

6.3.2 Evaluation of response to single agent selinexor (during cycle 1)

Unless there is evidence of progressive disease by examination of the blood, participants should undergo bone marrow aspiration on day 15 (± 2 days). This evaluation must be performed prior to administration of day 15 therapy.

6.4 Evaluations After Completion of Therapy

When a participant discontinues the study, a final visit will be conducted. Following discontinuation of the study treatment, the participant will be treated according to the investigator's discretion. If a participant discontinues from the study due to an adverse event considered related to study treatment, a follow-up visit should be conducted no later than 30 days after the last dose of protocol therapy. Safety assessments are recommended at least every 30 days, until all toxicities resolve, return to baseline or become clinically satisfactory, stable, or are considered irreversible.

7.0 OPTIONAL CORRELATIVE RESEARCH STUDIES

Summary information is provided below. Detailed information will be included in the laboratory manual to be provided by Karyopharm. Materials for collection and processing will also be provided by Karyopharm.

7.1 Optional Pharmacokinetic (PK) Studies - Plasma (*completed*)

Samples for pharmacokinetic (PK) analysis will be collected during Cycle 1 of the dose escalation portion of the trial.

7.1.1 Timing of PK samples

Day 1 dose of selinexor (single agent): prior to day 1 dose, and at 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 24 hours, and 48 hours after day 1 dose.

Day 22 dose of selinexor (to support combination kinetics): prior to day 22 dose and at 1 hour, 2 hours, 4 hours, and 8 hours after day 22 dose.

2 mL samples will be collected for each sampling point.

7.2 Optional Pharmacodynamic (PD) Studies (*completed*)

Samples for pharmacodynamic (PD) analysis will be collected during Cycle 1 of the dose escalation portion of the trial.

7.2.1 XPO1 expression levels

Measurement of XPO1 mRNA will be performed by Karyopharm as described in the lab manual. Whole blood will be collected from patients (2x2 ml), collected pre- and post-dosing (≥ 4 hr) and total RNA will be isolated to study changes in gene expression before and after exposure to selinexor. Inhibition of XPO1 (selinexor target) will be assessed by qRT-PCR of XPO1 and other genes, which are upregulated once XPO1 is inactivated (e.g., ARRDC3, NGFR, SLC family, PCLO) will also be analyzed. Please refer to Lab Manual for detailed instructions.

Timing of XPO1 expression samples

Whole blood samples (2x2.5 ml per time point) for leukocyte XPO1 analysis will be collected prior to the first dose of selinexor and at 4 hours, 8 hours, 24 hours, and 48 hours after the first dose.

7.2.2 Cytokine analysis

Blood samples (2 ml) will be collected pre- and post-dosing and analyzed for plasma cytokine concentrations. Cytokines include: IL1 α , TNF α , IL-6, MCP1, IFN γ , VEGF α , IL-8, IFN α , IL-10.

Timing of cytokine samples

Blood samples (2 ml per time point) for cytokine analysis will be collected prior to first dose of selinexor (within 10 minutes before administration) and 4 hours (\pm 20 min), 8 hours (\pm 30 min), 24 hours (\pm 2 hours), and 48 hours (\pm 2 hours) after the dose.

7.3 Optional Correlative Biological Studies (Phase II)

Preclinical studies have suggested that XPO1 expression is associated with disease outcome, p53 status may correlated with response, and subcellular protein localization may be predictive of response.^{6,20} Notably, two patients the phase I portion of this study became MRD negative after receiving only selinexor, indicating that there is a patient population who might benefit from single-agent selinexor therapy and would benefit from development of predictive tools.

Bone marrow aspiration (5 ml in EDTA) will be collected for research purposes at the planned disease evaluations prior to the start of therapy (but after consent), at the day 15 evaluation, and at the end of cycle 1 evaluation. Genomics studies prior to therapy will include whole-genome sequencing, whole-exome sequencing, and RNA-seq to fully characterize the leukemic cells. At subsequent time points, these studies will include whole-exome sequencing (or other targeted sequencing approaches) and RNA-seq to investigate how the leukemia cells are responding to therapy. In cases with a blast percentage of <50% at any time point, the blasts may need to be sorted by flow cytometry to enrich for the leukemic cell population to provide enough cells for analysis. Additional biologic studies may include chemical screens with assessment of apoptosis, assessment of subcellular protein localization, and the development of xenograft models to further characterize the leukemia response to selinexor.

8.0 EVALUATION CRITERIA

8.1 Response Criteria

Because morphologic examination of the bone marrow during periods of hematopoietic recovery after intensive chemotherapy may be unreliable, response will be based on blast

percentage by flow cytometry. Blast percentages determined by morphology will be used in cases that are not evaluable by flow cytometry.

8.1.1 Complete remission (CR)

- Bone marrow with < 5% blasts confirmed by flow cytometry
- ANC \geq 500/ μ L and platelets \geq 75,000/ μ L without transfusions
- No evidence of extramedullary disease

8.1.2 Complete remission with incomplete blood count recovery (CRi)

- Bone marrow with < 5% blasts confirmed by flow cytometry
- ANC < 500/ μ L or platelets < 75,000/ μ L without transfusions
- No evidence of extramedullary disease

8.1.3 Partial response (PR)

- Bone marrow with 5% to 25% blasts by flow cytometry and a decrease of at least 50% in blast percentage
- No evidence of extramedullary disease

8.1.4 No response (NR)

Participant fails to qualify for any of the categories listed above

8.1.5 Relapse

Subsequent appearance, after achievement of CR, of \geq 5% blasts in the bone marrow with confirmation by flow cytometry or the development of extramedullary disease after achievement of CR

8.2 Toxicity Evaluation Criteria

Common Terminology Criteria for Adverse Events v4 (CTCAE): This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the current version of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (<http://ctep.info.nih.gov>). Additionally, toxicities will be reported on the appropriate data collection screens.

9.0 OFF-TREATMENT AND OFF-STUDY CRITERIA

9.1 Off-Treatment Criteria

- Development of a DLT
- No response to therapy
- Relapse

- Second malignancy
- Treatment with other antineoplastic therapy or hematopoietic stem cell transplantation
- Development of unacceptable toxicity during treatment
- Refusal of further protocol therapy by participant, parent, or guardian
- Completion of protocol therapy

9.2 Off-Study Criteria

- Death
- Lost to follow up
- Withdrawal of consent

10.0 SAFETY AND ADVERSE EVENT REPORTING

10.1 REPORTING ADVERSE EXPERIENCES AND DEATHS

Principal investigators are responsible for promptly reporting to the IRB any adverse events that are unanticipated, serious, and that may represent potential harm or increased risk to research participants. When an unanticipated death occurs, the PI should report it to the Director of the Office of Human Subjects' Protection immediately, by phone: [REDACTED], Cell: [REDACTED], fax: [REDACTED], or e-mail: [REDACTED].

A reportable event entry into TRACKS should follow within 48 hours. Serious, unanticipated, and related or possibly related events will be reported within 10 working days.

The principal investigator is responsible for reviewing the aggregate toxicity reports and reporting to the IRB if the frequency or severity of serious toxicities exceed those expected as defined in the protocol or based on clinical experience or the published literature. Any proposed changes in the consent form or research procedures resulting from the report are to be prepared by the study team and submitted with the report to the IRB for approval.

The following definitions apply:

A **serious event** refers to any event in which the outcome is fatal or life-threatening, results in permanent disability, causes inpatient hospitalization or prolongs existing inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

An **unanticipated adverse event** refers to those not identified in their nature, severity, or frequency in the current risk documents (e.g., investigator's brochure), or consistent with the investigational plan.

The following are considered reportable: Any injuries, serious event or other unanticipated adverse events involving risk to participants or others which occur at a frequency above that considered acceptable by the investigators and the IRB. (FDA) As

described in 4.3 above, the OHSP Director or designee performs the initial review of unanticipated problems or serious adverse event reports. Internal reports of events that are unanticipated, serious, and related or possibly related to study interventions or procedures are then forwarded to the IRB Chair or designee and if necessary, referred to the full IRB. Based on the frequency and seriousness of adverse events, the IRB Chair or Committee may deem it necessary to suspend or terminate a research study or studies.

10.1.1 Reporting to Karyopharm

In addition to reporting to the FDA, St. Jude will forward completed SAE form to representatives of the Karyopharm Team:

[REDACTED]

It is the responsibility of St. Jude, the sponsor, to collect and document required information regarding Adverse Events (AEs) in accordance with all applicable laws and regulations.

St. Jude shall be responsible for ensuring that reports of Serious Unexpected Suspected Adverse Reactions (SUSARs) are prepared and submitted to the appropriate Regulatory Authorities, Competent Authorities, Institutional Review Boards (IRBs) and Ethics Committees (ECs) in accordance with applicable regulations and legislation.

For all SUSARs, St. Jude is responsible for providing a copy of the regulatory report (to include a MedWatch or CIOMS forms) to Karyopharm Therapeutics at [REDACTED] promptly - to mean as soon as is possible, and not more than 15 days from becoming aware of the event.

In addition to SUSAR reporting to Karyopharm, St. Jude is responsible for providing 6-month Adverse Reaction Reports (all AEs assessed as causality related to Karyopharm investigational product) to Karyopharm Therapeutics at [REDACTED] throughout the duration of the study. These reports are to contain listings of non-serious (expected or unexpected) adverse reactions and serious or non-serious expected adverse reactions which were collected during the 6-month report cycle.

St. Jude is responsible for obtaining any additional follow-up information regarding safety reports, upon request from Karyopharm.

KARYOPHARM THERAPEUTICS will inform St. Jude regarding any SUSAR detected in other clinical studies, ISTs, or compassionate use as promptly as is possible upon becoming aware of same.

10.2 Recording and Reporting AEs and SAEs

Adverse events (AEs) will be evaluated and documented by the clinical staff and investigators throughout inpatient hospitalizations and each outpatient visit. CRAs are responsible for reviewing documentation related to AEs and entering directly into CRIS

protocol-specific database. The data to be recorded are 1) the event description, 2) the NCI CTCAE v4.0 code and grade, 3) the onset date, 4) the resolution date (or ongoing), 4) action taken for event, 5) patient outcome 6) relationship of AE to protocol treatment/interventions, 7) if AE was expected or unexpected, and 8) comments, if applicable.

AEs that are classified as serious, unexpected, and at least possibly related will be notated as such in the database as “SAEs”.

Attribution of an Adverse Event

Not related- The lack of a temporal relationship of the event to study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation.

Unlikely related- The temporal relationship of the event to study treatment makes a causal relationship reasonably unlikely, and other drugs, therapeutic interventions or underlying conditions may not provide sufficient explanation for the observed event.

Possibly related- The temporal relationship of the event to study treatment makes a causal relationship reasonably possible, and the event is more likely explained by exposure to the study treatment than by other drugs, therapeutic interventions or underlying conditions.

For the purpose of safety analyses, all AE’s that are classified as unlikely or possible will be considered treatment-related events.

These events will be reported expeditiously to the St. Jude IRB within the timeframes as described above. Cumulative summary of Grades 2-5 events will be reported as part of the progress reports to IRB at the time of continuing review. Specific data entry instructions for AEs and other protocol-related data will be documented in protocol-specific data entry guidelines, which will be developed and maintained by study team and clinical research informatics.

Patients with abnormal blood counts due to bone marrow involvement by disease (i.e. all leukemia patients and lymphoma patients with bone marrow involvement) will be considered non-evaluable for hematological toxicities.

The study team will meet regularly to discuss AEs (and other study progress as required by institutional DSMP). The PI will review Adverse Event reports generated from the research database, and corrections will be made if applicable. Once the information is final the PI will sign and date reports, to acknowledge his/her review and approval of the AE as entered in the research database.

10.3 Process for Reporting Adverse Events From and To Collaborating Sites

Adverse events from collaborating sites will also be reviewed by the PI and discussed in study team meetings as described above. SAE reports from collaborating sites for AEs

that are serious, unexpected, and at least possibly related to protocol treatment or interventions will be reported to site IRB and the St. Jude IRB within the reporting requirements described above. The PI will determine if this is an event that will need to be reported expeditiously to all participating sites, considering the following criteria:

- Is the AE serious, unexpected, and related or possibly related to participation in the research?
- Is the AE expected, but occurring at a significantly higher frequency or severity than expected?
- Is this an AE that is unexpected (regardless of severity that may alter the IRB's analysis of the risk versus potential benefit of the research *and*, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document?

With the submission of the "Reportable Event" in St. Jude TRACKS application, the PI will indicate if all sites should be notified to report to their IRBs, and if the protocol and/or consent should be amended (consent will be amended if event is information that should be communicated to currently enrolled subjects).

Generally, only events that warrant an amendment to the protocol and/or consent will be reported expeditiously to all sites. However, any event may be reported expeditiously to all sites at the discretion of the PI.

A cumulative summary of Grade 2-5 AEs and expected/unrelated deaths that occur more than 30 days after protocol treatment will be reported to all sites with study progress report at the time of continuing review.

For collaborating sites: Serious AND unexpected events are to be reported to the St. Jude PI (Dr. Jeffrey Rubnitz) within 48-72 hours via fax or email.

Unexpected deaths must be reported to the St. Jude PI via phone call or email within 24 hours of the event. A written report must follow.

All correspondence and reports must also be sent by email to the **SELHEM study team**.

Jeffery E. Rubnitz, MD, PhD
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Leukemia/Lymphoma Division
St. Jude Children's Research Hospital
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Memphis, TN 38105
Phone: [REDACTED]
FAX: [REDACTED]
Email: [REDACTED]
Email: [REDACTED]

11.0 DATA COLLECTION, MONITORING AND CONFIDENTIALITY

11.1 Data Collection

Electronic case report forms (e-CRFs) will be completed by the clinical trials staff from the Cancer Center Comprehensive Center, Hematological Malignancies Program. Data will be entered from record directly into a secure CRIS database, developed and maintained by St. Jude Clinical Research Informatics.

Data Management will be supervised by the Director of Clinical Trials Management, and Manager of Clinical Research Operations for the Hematological Malignancies Program, working with Dr. Rubnitz or his designee. All protocol-specific data and all grade 2-5 adverse events will be recorded by the clinical research associates into the CRIS database, ideally within 2-4 weeks of completion of study phase. All questions will be directed to the attending physician and/or PI and reviewed at regularly-scheduled working meetings. Data collection for adverse events will be captured for 30 days after participant is removed from treatment, or until the participant receives other anti-leukemia therapy.

The attending physicians (or their designees) are responsible for keeping up-to-date roadmaps in the patient's primary SJCRH medical chart. Regular (at least monthly) summaries of toxicity and protocol events will be generated for the PI and the department of Biostatistics to review.

11.2 Study Monitoring

The Clinical Research Monitor will track accrual continuously and verify 100% of all data points on all study participants *quarterly* to assess overall study conduct, Human Subjects Protections, and the accuracy of database entries. Essential regulatory documents and all study documents including medical records, electronic media, database entries, study worksheets, and case report forms will be reviewed for recording and reporting of Adverse Events/Serious Adverse Events (SAEs) to include type, grade, attribution, duration, timeliness and appropriateness. Study documents are also reviewed for participant status, eligibility, the informed consent process, demographics, staging, study objectives, subgroup assignment, treatments, evaluations, responses, participant protocol status, off-study and off-therapy criteria, and for all other specifics as detailed in the protocol. The Monitor will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Monitoring may be conducted more frequently if deemed necessary by the CPDMO and/or the IMC.

Continuing reviews by the IRB and CT-SRC will occur at least annually. In addition, SAE reports in TRACKS (Total Research and Knowledge System) are reviewed in a timely manner by the IRB/ OHSP.

Source document verification of eligibility for all SJCRH cases will be performed within two weeks of completion of enrollment. This will include verification of appropriate documentation of consent. Monitoring of timeliness of serious adverse event reporting will be done as events are reported in TRACKS.

Monitoring of this protocol is considered to be in the high-risk 2 category (HR-2). The Monitoring Plan is outlined in a separate document from this protocol, but has been submitted for review and approval by the Clinical Trials Scientific Review Committee and the Institutional Review Board.

St. Jude affiliates and domestic collaborating study sites will be monitored on-site by a representative of St. Jude at intervals specified in the Data and Safety Monitoring Plan. International collaborators will be monitored by a Contract Research Organization (CRO), or other mechanisms according to the study-specific monitoring plan.

11.3 Confidentiality

Study numbers will be used in place of an identifier such as a medical record number. No research participant names will be recorded on the data collection forms. The list containing the study number and the medical record number will be maintained in a locked file and will be destroyed after all data have been analyzed.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, and clinical research monitors.

12.0 STATISTICAL CONSIDERATIONS

The primary objective of the phase I portion of this study is to determine a tolerable combination of selinexor, fludarabine, and cytarabine in patients with relapsed or refractory hematologic malignancies including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS). Although disease response to treatment will be explored, this phase I portion of the study is not designed to yield a formal evaluation of the efficacy of this regimen.

The primary objective of the phase II portion of the study is to estimate the overall response rate, as defined by complete response or complete response with incomplete count recovery, of selinexor in combination with fludarabine and cytarabine for patients with relapsed or refractory AML. This will be assess be assessing the null hypothesis that overall response rate is $< 30\%$, as specifically described below.

Responsible investigator: Jeffrey Rubnitz, MD, PhD
Responsible statistician: Stanley Pounds, PhD

12.1 Dose Escalation Phase

Evaluable for toxicity

Any participant who experiences dose-limiting toxicities (DLT) at any time during the first 35 days after taking the initial dose of selinexor and before receiving non-protocol therapy (such as transplant) is considered evaluable for toxicity. Participants without DLT who receive at least 5 of the 6 prescribed cycle I doses of selinexor and can be followed for 35 days following their initial dose of selinexor are also considered evaluable for toxicity. The evaluation period for purposes of determining whether a participant has a DLT will be the first 35 days following the initial dose of selinexor. Participants who are not evaluable for toxicity (such as those removed early from therapy to start alternate therapy) at a given dose level will be replaced.

Maximum tolerated dose (MTD)

The MTD is empirically defined as the highest dose level at which six participants have been treated with at most one participant experiencing a DLT and the next higher dose has been determined to be too toxic. If the lowest dose level studied is too toxic or the highest dose level studied is considered safe, the MTD will not have been considered estimated.

Dose escalation/de-escalation rules

The rolling-6 design²¹ will be used to determine dose escalation and reduction within each stratum separately. The rolling-6 design is described in greater detail below.

Two to six participants can be concurrently enrolled onto a dose level, dependent on 1) the number of participants enrolled at the current dose level, 2) the number of participants who have experienced DLT at the current dose level, and 3) the number of participants 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.

Decision as to which dose level to enroll a participant is based on the number of participants currently enrolled and evaluable, the number of participants experiencing DLT, and the number of participants still at risk of developing a DLT at the time of new participant entry. For example, when three participants are enrolled onto a dose level, if toxicity data is available for all three participants and no DLTs are observed when the 4th participants enter, the dose is escalated and the 4th participants is enrolled to the next higher dose level; if toxicity data is not yet available for one or more of the 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; if two or more DLTs have been observed from the three participants, the dose level is de-escalated. This process is repeated for the 5th and 6th participants. Accrual is only suspended when a cohort of six is filled. The starting dose of selinexor will be 30 mg/m²/dose. Table 3 of section 4.3 lists the dose levels to be explored in this study. Section 4.3.2 defines the dose limiting toxicity for this study.

12.2 Phase I Sample Size/Accrual Rate

As previously stated, the rolling-6 design will be applied. The minimum sample size of four occurs in the case that the first two patients on dose level 1 have a DLT, the dose is reduced and then the first two patients on dose level -1 have a DLT. The maximum sample size of 24 patients occurs if 6 patients are treated at each of the 4 dose levels. Thus, the total sample size may be as small as 4 and as large as 24 evaluable participants. The principal investigator estimates an annual accrual of 10 to 12 patients per year.

12.3 Phase II Sample Size/Accrual Rate

For purposes of this Phase II evaluation, we define a success as complete remission, complete remission with incomplete count recovery, or, for patients who are enrolled with <5% blasts, the achievement of MRD negativity, by the end of one course of therapy. Patients who die before reaching this milestone will be counted as failures for purposes of this Phase II design. We will use Simon's minimax two-stage design for the Phase II component.²² In the first stage, we will enroll 28 patients. Patients who have been enrolled on the dose expansion cohort and who meet the eligibility criteria for the Phase II portion of the study, will be included in the analysis. The study will stop at any point it becomes impossible to obtain 8 or more successes (CR or CRi or MRD negativity) among the first 28 patients. If 8 or more successes are observed among the first 28 patients, the study will continue to enroll an additional 11 patients for a total of 39 patients. For the phase I portion of the trial, we enrolled 18 patients in 15 months, for an accrual rate of 1.2 patients/month. Conservatively assuming each of the four additional participating sites enroll one patient per year, the accrual will increase to 1.5 patients/month. At this rate the study will be open for as little at 19 months or up to as long as 26 months.

12.4 Analysis of Secondary Objectives

Pharmacokinetic studies

Plasma samples will be analyzed via a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor concentration. Selinexor concentration data will be analyzed in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, concomitant medications, and treatment. Details of the population PK analysis, including software, post-processing and statistical analysis, will be outlined in a separate Data Analysis Plan, to be completed prior to database lock. Interim analysis may be conducted on draft plasma selinexor concentration data throughout the study. Summary statistics, including mean, median, standard deviation, coefficient of variation and group size may be compiled and reported during the study. Interim analysis of key selinexor PK parameters and key biomarker analyses may be performed in order to provide a pharmacokinetic-pharmacodynamic assessment throughout the study.

Efficacy

The efficacy of the combination of selinexor, fludarabine, and cytarabine, as measured by the complete response (CR) rate and the overall response (OR) rate (CR + CRi + PR) will be assessed for the patients enrolled at the RP2D. The rates of CR and OR will be presented as a point estimate with a 95% exact binomial confidence interval.

The therapy offered in the phase II portion of this protocol will be considered worthy of further study if success, as defined in section 12.3, is achieved for 16 or more of the 39 patients. This design has a 10% probability of declaring the therapy worthy of further study under the null hypothesis that the true success rate is 30%. This design has a 90% probability of declaring the therapy worthy of further study under the alternative hypothesis that the true success rate is 50%. This design was obtained by the R command *ph2simon*(*pu* = 0.3, *pa* = 0.5, *ep1*=0.1, *ep2*=0.1) defined in version 1.0.11 of the R package *clinfun*. The method of Koyama and Chen as implemented in the *twostage inference* procedure of the *clinfun* R package will be used to compute the confidence interval for the success rate.²²

Responsible investigator: Jeffrey Rubnitz, MD, PhD
Responsible statistician: Stanley Pounds, PhD

12.5 Analysis of Exploratory Objectives

Pharmacodynamic and correlative biological studies

Analysis of the pharmacodynamic and correlative biological studies will be descriptive.

Responsible investigator: Jeffrey Rubnitz, MD, PhD
Responsible statistician: Stanley Pounds, PhD

12.6 Anticipated Completion Dates

Anticipated primary completion date: December, 2018
Anticipated study completion date: January, 2020

13.0 OBTAINING INFORMED CONSENT

13.1 Consent Prior to Research Interventions

Initially, informed consent will be sought for the institutional banking protocol (TBANK research study), PGEN5, and for other procedures as necessary for standard medical care. During the screening process for eligibility, informed consent for SCREEN protocol OR for SELHEM is required before any research tests are performed.

13.2 Consent at Enrollment

The process of informed consent for SELHEM will follow institutional policy. The informed consent process is an ongoing one that begins at the time of diagnosis and ends after the completion of therapy. Informed consent should be obtained by the attending physician or his/her designee, in the presence of at least one non-physician witness. Initially, informed consent will be sought for the institutional banking protocol (research study), blood transfusion and other procedures as necessary. After the diagnosis of relapsed or refractory leukemia is established, we will invite the patient to participate in the SELHEM protocol.

Throughout the entire treatment period, participants and their parents receive constant education from health professionals at SJCRH and collaborating sites, and are encouraged to ask questions regarding alternatives and therapy. All families have ready access to chaplains, psychologists, social workers, and the St. Jude ombudsperson for support, in addition to that provided by the primary physician and other clinicians involved in their care. We will also obtain verbal assent from children 7 to 14 years old and written assent for all participants ≥ 14 years of age.

13.3 Consent at Age of Majority

Participants who reach the age of majority while on study will be re-consented for continued participation on SELHEM at the time of their next clinic visit after turning 18 year according to Cancer Center and institutional policy.

13.4 Consent When English is Not the Primary Language

When English is not the participant, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information will be documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information. The process for obtaining an interpreter and for the appropriate use of an interpreter is outlined on the Interpreter Services, OHSP, and CPDMO websites.

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APPENDIX I: SELINEXOR Dosing Guidelines

Phase II Cohort: Dose Level 2 (40 mg/m²)

BSA range	Total mg dose
0.45 – 0.55	20
0.56 – 0.68	25
0.69 – 0.81	30
0.82 – 0.93	35
0.94 – 1.06	40
1.07 – 1.18	45
1.19 – 1.31	50
1.32 – 1.43	55
1.44 – 1.56	60
1.57 – 1.68	65
1.69 – 1.81	70
1.82 – 1.93	75
1.94 – 2.06	80
2.07 – 2.18	85
2.19 – 2.31	90
2.32 – 2.43	95
2.44 and greater	100

APPENDIX II: PERFORMANCE STATUS CRITERIA

PERFORMANCE STATUS CRITERIA					
<i>Karnofsky and Lansky performance scores are intended to be multiples of 10</i>					
ECOG (Zubrod)		Karnofsky		Lansky	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction	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
1	Restricted in physically strenuous activity by ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	80	Normal activity with effort; some signs or symptoms of disease	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
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs	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
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	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
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair	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 III: TESTS PERFORMED FOR ROUTINE CARE AND FOR RESEARCH

Routine care

History & physical (including vital signs, BSA, PS)
CBC, differential, platelets
Serum chemistries
Amylase/lipase
Creatinine kinase, urate
TSH
Coagulation studies
GFR or creatinine clearance
Ophthalmologic exam
Pregnancy testing
EKG
Chest x-ray
Pulse oximetry
Lumbar puncture for IT chemotherapy, CSF cell count and differential
Bone marrow procedure for morphology, response assessment, MRD
Peripheral blood for MRD, if done
Commercially available agents – fludarabine, cytarabine, ITHMA

Research

Investigational agent – Selinexor
Pharmacokinetic studies (phase I only)
Pharmacodynamic studies (phase I only)
Correlative biological samples (phase II only)

APPENDIX IV: SELINEXOR DOSE MODIFICATION GUIDELINES FOR ADVERSE EVENTS ASSOCIATED WITH SELINEXOR

Toxicity and Intensity	Dose Modification
Fatigue (common)	
Grade 1	Insure adequate caloric intake and assess volume status. Adjust other medications. Consider addition of low dose corticosteroids (dexamethasone 5-10 mg/m ² /day with each dose of selinexor). Rule out other causes of fatigue such as adrenal insufficiency.
Grade 2	Insure adequate caloric and fluid intake and assess volume status. Add corticosteroids on day of selinexor (e.g., dexamethasone 5-10 mg/m ² /day). If fatigue dose not resolve to Grade 1, give dexamethasone on the day of <i>and</i> the day after selinexor dosing. If this does not improve fatigue, add a stimulant or bupropion q am, or reduce the dose of selinexor by one level (Table A2.1).
Grade 3	Insure adequate caloric and fluid intake and assess volume status. Initiate glucocorticoids as described for Grade 2. Interrupt selinexor dosing until resolved to Grade ≤ 2, reduce dose of selinexor by 1 level (Table A2.1), and add corticosteroids on day of and day after selinexor dosing.
Anorexia (common)	
Grade 1	Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure [®]). If fatigue or nausea also present, consider low doses of corticosteroids (as for fatigue) on day of ± day after selinexor dosing.
Grade 2	Add high-calorie supplements (e.g., Ensure [®]). Consider olanzapine 1.25 to 5 mg po qhs or mirtazapine 7.5-15mg po qhs (especially if nausea or sleep disturbance present). Consider megestrol acetate, 10 to 15 mg/kg/day; 800 mg/day maximum dose. Consider low dose corticosteroids (see fatigue), anabolic steroids such as oxandrolone, or dronabinol (Marinol [®]) or other cannabinoid. Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week. If Grade 2 anorexia does not resolve after institution of supportive medications, reduce selinexor dose by 1 level (Table A2.1).
Grade 3	Interrupt dosing with selinexor. Add high calorie supplements. Use supportive medications alone or in combinations. Restart selinexor at 1 dose level reduction (Table A2.1) once anorexia resolves to Grade ≤ 2. If Grade 2 anorexia persists with supportive medications, reduce dose of selinexor another level (Table A2.1).
Nausea - acute (common)	
Grade 1	5-HT ₃ antagonists, D ₂ antagonists, olanzapine 1.25 to 5mg daily, corticosteroids (e.g., dexamethasone 5-10 mg/m ² /day with each dose of selinexor ± the day after dosing), NK ₁ antagonists, or dronabinol (Marinol) or combinations can prevent nausea in the majority of patients.
Grade 2	Implement one or more combinations of anti-nausea medications. If nausea does not resolve to Grade ≤ 1, reduce dose of selinexor by one dose level (Table A2.1).
Grade 3	Implement one or more combinations of anti-nausea medications and interrupt dosing of selinexor. selinexor may be restarted with one dose level reduction (Table A2.1) when nausea is Grade ≤ 2 and adequate caloric and fluid intake have been achieved.

Hyponatremia (common)	
Grade 1 (Lower Limit of Normal to 130 nM)	Be certain sodium level is corrected for hyperglycemia (serum glucose >150mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH), Fanconi Syndrome, hyperglycemia, diuretic use). Maintain selinexor dose level, assure adequate fluid, electrolyte and caloric intake, adjust other medications, consider salt supplementation one – two times per day.
Hyponatremia 126-129nM without Symptoms (Grade 3)	Be certain sodium level is corrected for hyperglycemia. Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH), Fanconi Syndrome, hyperglycemia, diuretic use). Hold selinexor until Grade ≤ 1 (≥ 130 nM) and initiate aggressive salt supplementation two-three times per day.
Grade 3 (120-125 nM) or any Grade 3 with Symptoms	Be certain sodium level is corrected for hyperglycemia. Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH), Fanconi Syndrome, hyperglycemia, diuretic use). Hold selinexor until resolved to Grade ≤ 1 (≥ 130 nM) then reduce selinexor dose by 1 level. Initiate aggressive salt supplementation two-three times per day. If serum sodium stabilizes for at least 4 weeks, then original dose of selinexor may be resumed.
Diarrhea (common)	
Grade 1 (despite maximal anti-diarrheal medication)	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care, e.g., loperamide (Immodium®). Maintain dose level of selinexor.
Grade 2 (despite maximal anti-diarrheal medication)	Reduce to selinexor to one weekly until resolved to \leq Grade 1, then re-start twice weekly at the current dose level. If diarrhea returns as \geq Grade 2, then reduce selinexor dose by one dose level and dose once weekly until resolved to \leq Grade 1, then re-start twice weekly at reduced dose level
Grade 3/4 (despite maximal anti-diarrheal medication)	Delay selinexor until resolved to \leq Grade 2, then follow guidelines above.
Thrombocytopenia	
Grade 3 Thrombocytopenia Without bleeding	Implement platelet growth factors or transfusions. Begin (or maintain) once weekly dosing at the same dose level until resolved to Grade ≤ 2 .
Grade 4 Thrombocytopenia Without bleeding	Implement platelet growth factors or transfusions. Hold dosing until Grade ≤ 3 and follow above guidelines if Grade 3.
\geq Grade 3 Thrombocytopenia associated with petechiae or purpura	Implement platelet growth factors and/or transfusions. Hold selinexor for 5 days after last bleeding. Restart dosing one dose level below.
Neutropenia	
Grade 3 neutropenia without fever	Implement growth factors.
Grade 4 neutropenia without fever	Implement growth factors. If appropriate, initiate prophylactic anti- microbial agents.
Grade ≥ 3 febrile neutropenia	Implement growth factors. Initiate appropriate broad spectrum anti- microbial agents. Hold selinexor until fever resolves and patient is clinically stable. Restart dosing one dose level below.

Other selinexor-related adverse events	
Grade 1 or 2	Maintain dose level and initiate standard supportive care.
Grade 3	Delay dose until resolved to \leq Grade 1, then reduce by 1 dose level (Table A2.1).
Grade 4	Discontinue selinexor and rule out other causes. If other causes of Grade 4 adverse event are uncovered, selinexor may be re-initiated at 1 dose level reduction (Table A2.1).
<p>All dose modifications should be based on the worst preceding toxicity. Isolated values of \geq Grade 3 alkaline phosphatase values will NOT require dose interruption. Determination of liver vs. bone etiology should be made, and evaluation of gamma-glutamyl transferase (GGT), 5'-nucleotidase (5'NT), or other liver enzymes should be performed. Patients are allowed dose reductions to a minimum dose of 15 mg/m² as described in Table A2.1. a. Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) otherwise specified values.</p>	

APPENDIX V – SPECIMEN SUBMISSION GUIDELINES

Diagnostic studies

Morphology review

Central review of morphology is not required. However, Dr. John Choi [REDACTED] is available for review or assistance if requested by any collaborating site.

Cytogenetic review

Conventional karyotyping will be performed at local institutions as needed and the results will be reviewed by Dr. Susana Raimondi at St. Jude. Please submit two karyotypes of each abnormal line (this can be done electronically) and a final report to the following:

Dr. Susana Raimondi
Department of Pathology
St. Jude Children's Research Hospital
262 Danny Thomas Place
Memphis, TN 38105
Phone: [REDACTED]
FAX: [REDACTED]
Email: [REDACTED]

Immunophenotyping and molecular studies

Immunophenotyping for diagnostic purposes may be performed at local institutions or centrally, as desired by the treating physician. If the local institution prefers immunophenotyping to be done at St. Jude, please indicate this at the time the diagnostic bone marrow is shipped. Immunophenotyping to determine a leukemic-specific phenotype for future MRD studies will be performed at St. Jude.

Molecular studies may be performed at local institutions or centrally, as desired by the treating physician. The Molecular Pathology laboratory at St. Jude (Dr. Sheila Shurtleff, technical director) will carry out molecular studies as needed. AML cases may be tested for the presence of the *CBF-beta/MYH11*, *RUNX1/RUNX1T1* (*AML-1/ETO*), *MLL/MLLT3* (*MLL/AF-9*) and *MLL/MLLT4* (*MLL/AF-6*) fusion transcripts, *FLT3*-ITD, and mutations in the *FLT3*, *NPM1*, and *CEPBA* genes. Selected cases will also be screened for the presence of *MLL* gene rearrangements by FISH and for the *MLL-ENL*, *MLL-ELL*, *MLL-AF10*, or *RBM15/MKLI* fusions as needed.

At diagnosis, please collect a minimum of 10 mL of anticoagulated bone marrow (preservative free heparin). Place in a 15 mL sterile conical centrifuge tube and add 5 mL of sterile RPMI-1640 with 20% fetal calf serum (bovine serum albumin). Label the tube(s) with patient name, date of birth, and date sample obtained. Seal centrifuge tube with parafilm or equivalent. Complete the SELHEM Specimen Submission Form and

include with specimen(s) for shipping. Clinical specimens with a low probability of containing an infectious agent must be “triple packaged” in accordance with Dangerous Goods Regulations (DRG), International Air Transport Association (IATA) and OSHA guidelines (see <http://www.iata.org>, <http://osha.gov>, and AML08 Submission Form for additional information). Specimens should be shipped at ambient temperature.

Note: If bone marrow is unattainable (dry tap) or is less than 5 mL, peripheral blood containing leukemic blasts should be submitted along with any bone marrow obtained. 5 to 10 mL of peripheral blood collected in preservative free heparin should be added to RPMI 1640 with 20% FCS or BSA, processed and packaged for shipment as described for bone marrow specimens.

Ship by Federal Express for next day delivery to:

Tissue Resources
Department of Pathology, Room C5013B
St. Jude Children’s Research Hospital
262 Danny Thomas Place
Memphis, TN 38105

Phone: [REDACTED]

Email: [REDACTED]

*Please include FedEx tracking number

Please notify the Tissue Resources lab (Matthew Lear, technical director, [REDACTED]) and Dr. John Choi ([REDACTED]) via email when shipping MRD samples.

Minimal Residual Disease studies (required)

At Day 15 and all subsequent time points, please send 5 ml of bone marrow for MRD studies. Samples for MRD should be sent to the Tissue Resources Lab in preservative-free heparin stored at ambient temperature. In addition, for patients with leukemia-specific fusion transcripts, all bone marrow aspirates should be sent for RT-PCR analysis.

Note that MRD studies are not performed on weekends. Hence, samples for MRD should be drawn Monday through Thursday and sent by overnight delivery. MRD samples that arrive on weekends are processed on Monday, but such delay may affect the quality of the assay. Only diagnostic specimens will be accepted on weekends and holidays with prior notice.

Please notify the Tissue Resources lab and Dr. John Choi ([REDACTED]) via email when shipping MRD samples.

Correlative Biological Studies (optional)

Bone marrow aspiration (5 ml in EDTA) will be collected for research purposes at the planned disease evaluations prior to the start of therapy (but after consent), at the day 15 evaluation, and at the end of cycle 1 evaluation.

Ship by Federal Express for next day delivery to:

Tissue Resources
Department of Pathology, Room C5013B
St. Jude Children's Research Hospital
262 Danny Thomas Place
Memphis, TN 38105

Phone: [REDACTED]
Email: [REDACTED]

*Please include FedEx tracking number

Please notify the Tissue Resources lab (Matthew Lear, technical director, [REDACTED]) and Dr. Thomas Alexander [REDACTED] via email when shipping correlative biological samples.