An Investigator Sponsored Phase I/II Study of CLAG + Selinexor in Relapsed or Refractory Acute Myeloid Leukemia

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Protocol Revision History

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SCHEMA

Design Overview: This phase I/II investigator sponsored study will consist of a phase I portion (N= maximum of 24 patients) that evaluates an initial dosing schedule (Schedule A) followed by a more intense dosing schedule (Schedule B) at the same dose of selinexor. Once the optimal schedule is determined, the phase II study will evaluate the efficacy of this schedule in 40 patients (inclusive of 12 phase I patients), for a maximum total study population of 52 patients. Optional maintenance phase of single-agent selinexor is also allowed. All dosing cycles are 28 days long and the DLT evaluation period for phase I is during Cycle 1 of Schedules A and B. Prolonged myelosuppression, i.e., marrow cellularity < 5% on Day 42 or later (6 weeks) from start of Cycle 1 without any evidence of leukemia, will also be considered a DLT.

The phase I study uses a Bayesian design and allows for a 6 patient schedule de-escalation cohort in addition to the dosing of 6 patients on each schedule. The phase II portion was designed to compare the primary endpoint of complete remission rate (CR + CRi) with an historical rate of 33%. With a sample size of 40, it will have 80% power (0.05 significance level) to detect a difference from the historical rate if the study observes a CR/CRi rate $\geq$ 0.55.

Phase I Schedule A: Selinexor will be dosed on Days 1, 5, 10, and 12 of the 28-day cycle. All doses will be 60 mg each.

Phase I Schedule B: Selinexor will be dosed on Days 1, 5, 10, 12, 17, and 19 of the 28-day cycle. All doses will be 60 mg each.

Phase II: Selinexor will be given at the schedule as determined in phase I.

Selinexor (S):	Selinexor will be administered at 60 mg PO
Cladribine (CL):	5 mg/m^2/day IV once daily on Days 4-8
G-CSF (G):	300 mcg SC once daily on Days 3-8
Cytarabine (A):	2000 mg/m^2/day IV once daily on Days 4-8
Bone marrow biopsy/aspirate (BM):	Will be performed at baseline/screening, on Day 3, at the time of hematopoietic recovery, and as clinically indicated to assess treatment response. Additionally, samples will be banked for genomic studies indicated to document presence of persistent disease.
Peripheral blood (PB):	Will be performed at baseline/screening, on Day 3, on Day 5, on Day 7, and at the time of hematopoietic recovery.

The initial cohort of patients (N=6) will be dosed according to Schedule A. If dose limiting toxicities (DLTs) are not experienced with the initial cohort of patients, then dosing will be intensified whereby a further cohort of patients (N=6) will be treated with Schedule B dosing. The phase II dosing schedule will be the most intense schedule in which ≤3 DLTs are observed in 12 patients treated using that schedule. Patients in the phase I portion of the study treated at the MTD will count towards the phase II accrual goal for evaluation of the primary endpoint. Phase II will include a sample size of 40 patients.

Schedule A dosing:

Day	1	2	3	4	5	6	7	8	9	10	11	12
	S				S					S		S
			G	G	G	G	G	G				
				A	A	A	A	A				
				CL	CL	CL	CL	CL				
BM			BM									
PB			PB		PB		PB					

Schedule B dosing:

Day	1	2	3	4	5	6	7	8	9	10	11	12	17	19
	S				S					S		S	S	S
			G	G	G	G	G	G						
				A	A	A	A	A						
				CL	CL	CL	CL	CL						
BM			BM											
PB			PB		PB		PB							

In both the phase I and II portions of the study, patients are candidates for selinexor single agent maintenance therapy if they have achieved a CR or CRi based on post-treatment bone marrow assessment at the time of hematopoietic recovery and are either (1) transplant ineligible (defined in Section 5.6) or (2) do not have a stem cell transplant donor available. Prior to initiating maintenance therapy with selinexor, a bone marrow biopsy must confirm the presence of the CR or CRi. Maintenance therapy consists of 60mg selinexor on Days 1, 8, 15, and 22 of a 28 day cycle (4 doses per cycle), continuously until disease relapse, unacceptable toxicity, death, or the institution of additional antileukemic therapy including stem cell transplantation or donor leukocyte infusion.

Maintenance dosing:

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	S							S						
Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
	S							S						

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1 BACKGROUND AND RATIONALE

1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) represents a heterogeneous group of diseases characterized by infiltration of the bone marrow, blood, and other tissues by neoplastic hematopoietic cells. It represents the most common form of acute leukemia in adults, with an estimated 11,930 new cases in the United States each year.[1] The median age at presentation is 65, with a male:female ratio of approximately 5:3.[2] Without treatment, the disease ultimately progresses and is rapidly fatal within months.[3]

AML can be further classified based on molecular genetic and chromosomal abnormalities. Additionally other factors like age, performance status, presence of de-novo versus secondary AML, and laboratory parameters influence prognosis.[3,4]

Standard induction chemotherapy in AML consists of the "7+3" regimen with 7 days of continuous infusion cytarabine and 3 days of daunorubicin or idarubicin. This approach is followed by consolidation therapy including a hematopoietic stem cell transplant (HSCT) in those with high-risk disease. Intensive treatment regimens lead to complete remission (CR) in 60-80% of younger patients with de novo AML.[5] Unfortunately, for elderly patients (defined as those over age 60) CR rates are generally 40-50% with such therapy.[6] The median overall survival for those not attaining a CR is less than one year, with patients often succumbing to fatal complications related to bone marrow aplasia and impaired hematopoietic recovery.[7]

For those that do attain a CR, the majority will recur within three years of diagnosis.[8] The prognosis for those with relapsed or refractory AML remains poor. Aside from patients with specific AML subtypes (core-binding factor positive AML and acute promyelocytic leukemia), those with relapsed or primary refractory AML are unlikely to be cured without an allogeneic stem cell transplant. While select patients may move on to allogeneic stem cell transplant in first relapse, the majority will require reinduction chemotherapy prior to transplantation in order to attain disease control. In general, factors such as the duration of first remission, FLT3 mutational status, and the presence of high-risk cytogenetics have borne out as major prognostic markers in determining who is likely to respond to salvage chemotherapy.[9] Specifically, patients relapsing within one year of achieving a first remission and those patients who have unsuccessfully received a prior salvage regimen are unlikely to experience a second complete remission (CR rates 0-20%).[10,11]

Commonly utilized salvage regimens include high dose cytarabine alone; fludarabine, cytarabine, and G-CSF (FLAG); mitoxantrone, cytarabine, and etoposide (MEC); cladribine, cytarabine, and G-CSF (CLAG); and, for those who attained a long disease remission, initial induction therapy may be used as a salvage regimen.[12-15] Despite advances in supportive care and chemotherapy, 2 year overall survival is still poor in this population (12-58%); thus novel treatment approaches are needed for remission induction.[9]

In a single-center retrospective study of salvage chemotherapy in relapsed/refractory AML, the CLAG regimen showed a CR rate of 38% with an approximately 10% 30-day death rate.[16]

1.2 Nuclear Export

It has been shown that neoplasms must inactivate most or all of the major tumor suppressor proteins (TSP) and growth regulatory proteins (GRP) in order to perpetuate their phenotypes.[17] The vast majority of TSP and GRP require nuclear localization in order to carry out their antineoplastic and regulatory activities and therefore nuclear export leads to their functional inactivation. Nuclear import and export is a tightly regulated process facilitated by shuttle proteins in eukaryotic cells. There are over 15 nuclear import proteins, or importins, but only seven nuclear export proteins, or exportins (Exportins 1-7). The protein Exportin 1 (XPO1, also called CMR1) is known to be largely responsible for the export of major TSP and other growth modulators. Furthermore, XPO1 levels have been shown to be elevated in both solid and hematologic malignancies and higher levels generally correlate with poorer prognosis.[18-23] It appears that tumor cells have co-opted XPO1 to move TSP and GRP out of the nucleus, thereby neutralizing their anti-neoplastic functions.

XPO1 inhibitors block the nuclear export of key TSP, thereby leading to accumulation of these proteins in the nucleus, as nuclear import appears to proceed unimpeded. It has been shown that nuclear retention appears to prevent proteasome-mediated degradation (which is typically cytoplasmic). Forced nuclear retention of TSP and GRP can counteract a number of oncogenic (and inflammatory) pathways that perpetuate the neoplastic phenotype (Table 1.1). Moreover, certain proteins, specifically survivin and $p21^{CIP1}$ can be anti-apoptotic when localized to the cytoplasm and therefore forcing their nuclear retention with XPO1 inhibition can prevent their anti-apoptotic functions, and in the case of p21, expose its antitumor activities.[24,25]

Table 1.1 Effect of XPO1 Inhibition on Oncogenic and Inflammatory Pathways

Pathway Affected	Effect of XPO1 Inhibition	Reference
p53 mutation	p73 activation, p21 activation	26
MDM2 activation	Nuclear p53 retention and activation	23
NPM1 mutation	Restoration of nuclear NPM1	33
CEBPA down-regulation	Nuclear retention and activation	26
XPO1 overexpression	XPO1 reduction	34
FLT3 activation	FLT3 reduction	26
KIT activation	KIT reduction	26
NF-κB activation	IκB nuclear retention and activation	21
PIK3 or AKT activation	FOXO1, -3, -4 activation	21
Survivin – cytoplasmic	Survivin nuclear retention	35
Bcr-Abl activation	PP2A activation	34

1.3 Selinexor (KPT-330), a Selective Inhibitor of Nuclear Export / SINE™ Compound

Selinexor is an oral, first in class, slowly-reversible, potent and Selective Inhibitor of Nuclear Export / SINE™ compound that specifically blocks the protein Exportin 1 (XPO1), also known as chromosomal region maintenance 1 (CRM1). To date, other than XPO1, no targets of selinexor have been identified and XPO1 is overexpressed 2-4 fold in all cancers studies to date.

Selinexor restores many of the TSP and GRPs to the nucleus where they can carry out their normal regulatory and anti-tumor functions. Selinexor has shown to be selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both in vitro and in vivo. The nuclear export of eIF4E, a protein that binds to the mRNAs of many oncogenic and growth-promoting mediators, requires XPO1 for transport to cytoplasmic ribosomes. Selinexor blocks the XPO1-mediated nuclear export of eIF4E, preventing translation of the eIF4E-bound mRNAs on ribosomes, with a reduction in levels of the cognate oncogenic and growth-promoting proteins.

All cell types exposed to SINE™ in vitro undergo G1/S ± G2/M cell cycle arrest, followed by a 'genomic fidelity' review, and 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 directly cytotoxic to cells; rather, they can restore the highly effective tumor suppressing pathways that lead to selective elimination of genetically damaged (i.e., neoplastic) cells. Hematopoietic tumors are particularly susceptible to induction of apoptosis by XPO1 inhibition whereas normal hematopoietic cells and their functions are largely spared.

1.3.1 Preclinical Information

AML cells overexpress the nuclear exporter, Exportin 1 (XPO1/CRM1) and higher XPO1 levels generally correlate with poor outcome.[23] The novel Selective Inhibitor of Nuclear Transport / SINE™, selinexor, antagonizes XPO1 and shows potent cytotoxicity for AML and ALL cells *in vitro*, independent of genotype.

Selinexor shows potent antiproliferative effect and induced apoptosis, cell cycle arrest and myeloid differentiation in AML cell lines and patient blasts, including those from patients with NPM1 and FLT3-ITD mutations.[26]

Mechanistic studies show that SINE™ compounds induce nuclear localization and activation of multiple TSPs, leading to rapid apoptosis of AML cells. In addition, a strong down-regulation of the oncogenes FLT3 and c-KIT were observed after SINE™ treatment in both FLT3-ITD and wild-type cell lines.[26] Selinexor treatment also restored the localization of cytoplasmic mutant NPM1 into the nucleus.

In murine AML and acute lymphoblastic leukemia (ALL) models, selinexor showed potent antileukemic activity without toxicity to normal hematopoietic cells.[26,27]

In vitro experiments with continuous (~72 hour) exposure to selinexor demonstrated potent proapoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture including multiply-resistant cancers, with the majority of inhibitory concentrations, 50% (IC_{50}s) for cytotoxicity < 800 nM and most hematologic tumor lines having IC_{50}s of 20-400 nM for selinexor. Moreover, selinexor demonstrated cytotoxicity in multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) cells in the absence or presence of bone marrow stroma cells (BMSC). In contrast, normal cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC_{50}s were typically > 5 μM. As noted above, selinexor had little effect on normal (nonmalignant) lymphocytes or other nontransformed 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 (GI) dysfunction.

Selinexor, as well as other SINE™ compounds, was administered in efficacy studies to mice and dogs and in toxicology studies to rats and monkeys. The dosing regimen was every other day x 3 each week (QoD x3/wk); anti-tumor activity has also been shown with twice weekly (BIW, Days 1 and 4 of each week) dosing. Efficacy was demonstrated at doses of 5-20 mg/kg (15-60 mg/m^2) in mouse models of myeloma, mantle cell lymphoma (MCL), and T-cell acute lymphocytic leukemia (T-ALL) xenografts.

Selinexor demonstrated efficacy in numerous preclinical models of hematological and solid tumors (Azmi *et al.*, 2013a; Azmi *et al.*, 2013b; Cheng *et al.*, 2014; Etchin *et al.*, 2013a; Fragomeni *et al.*, 2013; Tai *et al.*, 2014; Walker *et al.*, 2013). Selinexor treatment resulted in significant survival advantages in models of MM, NHL, CLL, AML and ALL. Selinexor also demonstrated robust single agent efficacy in solid tumor xenografts including: prostate, breast, melanoma, colon, ovarian, neuroblastoma and several sarcomas. In addition, marked synergy was observed when selinexor was used with a variety of chemotherapies and targeted therapies including platinums, taxanes, topoisomerase I and II inhibitors, dexamethasone, cytarabine, proteasome inhibitors and various tyrosine kinase inhibitors (TKIs).

Preclinical parameters were assessed in three species: mouse (CD1), rat (Sprague-Dawley), and monkey (cynomolgus). While pharmacokinetic (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, and was 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. See the Selinexor Investigator's Brochure for more information.

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^{TM} compounds.

1.3.2 Clinical Experience

Study KCP-330-001 is a Phase 1, open-label, dose-escalation study to evaluate the safety and tolerability of oral selinexor and determine the recommended phase II dose in patients with advanced hematological malignancies. Arm 1 of this study includes patients with "chronic" hematological malignancies including multiple myeloma (MM), Waldenström's Macroglobulinemia (WM), Non-Hodgkin's Lymphoma (NHL) and chronic lymphocytic leukemia (CLL). 2 patients were enrolled in cohort 1 with dose escalation of 100% increase from cohort 1 to 2. Cohort 2 enrolled at least 3 patients with dose escalation of 100% increase from cohort 2 to 3. For cohorts 3 and beyond, a standard 3+3 design was used with dose escalation increase of 30-40% from the previous cohort.

Arm 2 includes patients with acute myeloid leukemia (AML) except M3 subtype. Due to the rapidly progressive nature of AML, Arm 2 began dosing at 16.8 mg/m^2 after dose limiting toxicity (DLT) clearance of 12 mg/m^2 in cohort 3 and after dosing at 16.8 mg/m^2 was employed in cohort 4 of the Chronic hematological malignancies portion of the study. A standard 3+3 design was used with a dose escalation increase of 30-40% from previous cohort. Arm 3 includes up to 12 patients with relapsed/refractory Peripheral T-cell lymphoma (PTCL) or Cutaneous T-cell lymphoma (CTCL) treated at a dose of 30 mg/m^2 twice weekly.

As of 10 June 2014, a total of 186 patients have been enrolled in this study, with 65 patients on Arm 2 (AML) enrolled at ten clinical centers in the USA, Canada, and Denmark, and treated at doses ranging from 3 mg/m^2 to 70 mg/m^2 on Schedule 2 or Schedule 3 (10 or 8 doses/cycle). As of 10 June 2014, 6 AML patients remain on study treatment.

Overview of Clinical Efficacy in AML. In Arm 2 (AML), 32 of the 48 patients (67%) evaluated as of 10 June 2014 have experienced a complete remission (CR), complete remission without platelet recovery (CRi), partial response, morphologic leukemia free state or stable disease (SD). Seven patients experienced a CR or CR(i). Five of these patients experienced a CR, while the other two patients experienced a CR(i). As of 10 June 2014, 1 patient has experienced a partial response, two of these patients showed a morphologic leukemia free state, 22 patients are showing SD. Seventeen patients were non evaluable as of 10 June 2014. Responses for the 48 patients who had been evaluated as of 10 June 2014, each of whom received a dose between 16.8 mg/m^2 to 70 mg/m^2 per cycle, are shown in Table 1.2.

Table 1.2 Responses in Arm 2 (AML) [16.8 mg/m^2 to 70 mg/m^2] as of 10 June 2014 (Study KCP-330-001)

Number of Patients Evaluated	Total CRs, CR(i)s, PR and SD (%)	CR (%)	CR(i) (%)	PR /MLFS (%)	SD (%)	PD (%)	WC (%)
48	32 (67%)	5 (10%)	2 (4%)	3 (6%)	22 (46%)	16 (33%)	2 (4%)

Abbreviations: N=number of patients, CR=complete remission, CRi=complete remission without platelet recovery, PR/MLFS= partial response / morphologic leukemia free state, SD=stable disease, PD=progressive disease, WC=withdrew consent.

Overview of Clinical Safety in AML. Gastrointestinal adverse events and fatigue are the most common types of AEs seen in Arm 2 (AML) patients. As of 2 May 2014, Karyopharm has reports of AEs in 54 of the 65 patients enrolled in this arm and the AE prevalence percentages below are based upon 65 patients. As of 2 May 2014, the gastrointestinal adverse events typically consist of nausea in 27 patients (42%), anorexia in 26 patients (42%), diarrhea in 23 patients (35%), vomiting in 17 patients (26%), and weight loss in 11 patients (17%). The gastrointestinal events are primarily Grade 1 or Grade 2 events that are generally responsive to standard supportive care. Fatigue was observed in 31 patients in this arm (48%) as of 2 May 2014, including Grade 3 fatigue in five patients (8%) and Grade 1 or Grade 2 fatigue in 26 patients (40%). Karyopharm observed Grade 4 thrombocytopenia in four patients (6%) in this arm as of 2 May 2014. Karyopharm expects that the thrombocytopenia is primarily a result of patients entering this arm with marked bone marrow suppression due to both disease and prior therapies. Karyopharm also observed Grade 4 neutropenia in four patients (6%) and Grade 4 anemia in one patient (>2%).

It is anticipated that fewer and more mild gastrointestinal events and reduced fatigue will be observed in the future as a result of the initiation of supportive care and medications prior to beginning selinexor therapy.

1.3.3 Potential Risks

Selinexor is currently in clinical development and has not been approved by the Food and Drug Administration (FDA) for commercial use. Human experience

with Selinexor is currently limited and the entire safety profile is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. Toxicity grading will be performed in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 4.03. If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All adverse events (AEs) and serious adverse events (SAEs) will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

Please refer the Investigator's Brochure for the most up-to-date information.

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. It is not anticipated that female patients enrolling in this study will be able to conceive. However, in the rare event that this is possible, female patients 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, effective methods of contraception must be used throughout the study and for three months following the last dose.

1.4 Study Rationale

Selinexor has shown single-agent activity in a current phase I study enrolling patients with relapsed/refractory AML with durable complete remissions (CR), complete remissions with incomplete hematologic recovery (CRi), partial remissions (PR), and stable disease (SD) observed. Furthermore, common toxicities included nausea, fatigue, and anorexia and were manageable with supportive care agents. Additionally, CLAG chemotherapy has proven activity in relapsed and refractory AML, and has been shown to be a relatively well tolerated regimen without significant non-hematologic toxicity.[16,28,29] Given the established role of CLAG chemotherapy, the single agent activity of selinexor, and their non-overlapping toxicities, we propose a phase I/II open label study of selinexor in combination with CLAG for the treatment of patients with relapsed/refractory AML.

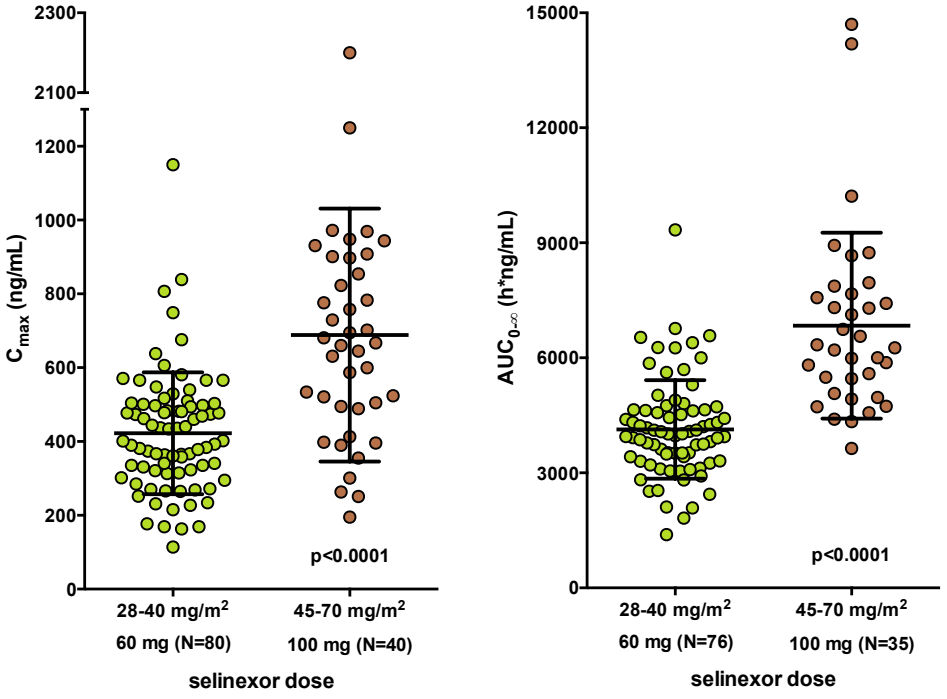
1.5 Rationale for Doses and Dosing Regimen

Greater than 450 patients with advanced cancers have been treated with oral selinexor in three Phase I studies. KCP-330-001 is a dose escalation study in patients with advanced hematologic malignancies including AML. KCP-330-002 is a dose escalation study in patients with advanced solid tumors. KCP-330-003 is a food effect study in patients with advanced sarcomas. Ten doses per 4-week cycle of selinexor were initially evaluated in studies. With this dosing regimen, the DLTs were anorexia, nausea, and fatigue at 40 mg/m^2 in KCP-330-002 and the maximum tolerated dose (MTD) was 30 mg/m^2 using this regimen. However, pharmacodynamics analyses suggest that at doses > 12 mg/m^2, selinexor inhibits XPO1 activity for > 48 hrs. Therefore, reduced intensity dosing at twice weekly was evaluated and subsequently showed improved tolerability with observed anti-cancer activity.

Selinexor therapy will be dosed based on a fixed oral dose of 60mg of selinexor, roughly equivalent to 35 mg/m^2. To ensure that no patient will be dosed at a dose >70mg/m^2, the study will be limited to patients with a body surface area (BSA) (calculated by Dubois method) >1.43 m^2. This dosing regimen is supported by the accumulated PK data to date (Figure 1.1) and summarized below.

The 5th and 95th percentile for BSA values encountered to date in Phase 1 trials KCP-330-001 and KCP-330-002 are 1.5 and 2.3 m^2, respectively (N=331). For this range, flat doses of 60 mg and 100 mg of selinexor translate to BSA normalized dose ranges of 27-40 mg/m^2 and 43-70 mg/m^2, respectively. To evaluate PK for flat doses of 60 mg and 100 mg of selinexor, Cmax and AUC(0-∞) values were compared for the equivalent, typical BSA-normalized dose ranges (Figure 1.1). Both Cmax and AUC(0-∞) were found to be significantly different ($p<0.0001$) for 60 mg and 100 mg of selinexor. Therefore, we conclude that 60 mg and 100 mg selinexor doses are expected to provide significantly different PK results.

Figure 1.1 Pharmacokinetic Results for 60 mg and 100 mg selinexor Doses



Comparison of C_{max} and $AUC_{(0-\infty)}$ for 60 mg and 100 mg selinexor doses based upon data from BSA-normalized doses for the typical range of BSA encountered in Phase 1 trials KCP-330-001 and KCP-330-002. Lines on plots represent mean and standard deviation P values are based upon unpaired t-test without assuming equal standard deviation.

1.6 Planned Correlative Studies

These summaries are not meant to be comprehensive but rather provide a high level overview of the correlative research undertaken here.

As selinexor induces cell cycle arrest and rapid apoptosis, we will quantify the bone marrow blast percentage, annexin V/7AAD, and cell cycle status in these samples by flow cytometry approximately 48 hours after selinexor administration through bone marrow aspirate and peripheral blood studies on Day 3.

To evaluate XPO1 expression, we will perform western blot and qRT-PCR assays for XPO1 using flow sorted AML blasts (CD45dimSSClo).

In order to further evaluate nuclear transport inhibition, we will examine if selinexor induces nuclear accumulation of some targets (p53, NPM, Fox03a, IκB, others) in AML blasts.

Pharmacokinetic analysis will be analyzed for the concentration of selinexor using a validated HPLC/MS-MS method through bone marrow aspirate and peripheral blood

studies on Day 3. Potential covariates include, but are not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, and concomitant medications. Pharmacodynamic biomarkers, including XPO1 inhibition may be added as covariates in the PK analysis in order to investigate potential pharmacokinetic/pharmacodynamics relationships.

2 OBJECTIVES

2.1 Primary Objectives

Phase I: To determine the safety and tolerability of selinexor + CLAG in patients with relapsed or refractory AML that requires treatment.

Phase II: To determine the complete remission rate (CR + CRi) for selinexor + CLAG in patients with relapsed or refractory AML that requires treatment.

2.2 Secondary Objectives

1. To determine the time to hematologic recovery (neutrophils and platelets) of patients with relapsed or refractory AML treated with selinexor + CLAG.

2. To determine the event-free survival of patients with relapsed or refractory AML treated with selinexor + CLAG.

3. To determine the duration of remission of patients with relapsed or refractory AML treated with selinexor + CLAG.

4. To determine the relapse-free survival of patients with relapsed or refractory AML treated with selinexor + CLAG.

5. To determine the overall survival of patients with relapsed or refractory AML treated with selinexor + CLAG.

6. To determine the number of patients with relapsed or refractory AML treated with selinexor + CLAG who were able to undergo hematopoietic stem cell transplantation

2.3 Exploratory Objectives

1. To characterize the effects of selinexor on nuclear transport inhibition and changes in XPO1 expression of patients with relapsed or refractory AML treated with selinexor + CLAG.

2. To evaluate the effects of selinexor on cell cycle arrest and apoptosis in patients with relapsed or refractory AML treated with KPT-330.

3. To determine the pharmacokinetics and pharmacodynamics of selinexor.

3 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically confirmed AML (defined using WHO criteria) with one of the following:
    a. Primary refractory disease following ≤ 2 cycles of induction chemotherapy, or
    b. First relapse with no prior unsuccessful salvage chemotherapy, or
    c. Relapsed or refractory to hypomethylating agent, defined as a lack of response, disease progression, loss of response, or intolerance as deemed by the study investigator

2. Age between 18 and 70 years old.

3. ECOG performance status ≤ 3 (see Appendix 1).

4. Adequate organ function as defined below:
    a. AST(SGOT), ALT(SGPT), total bilirubin ≤ 2 x IULN except when in the opinion of treating physician is due to direct involvement of leukemia (eg. hepatic infiltration or biliary obstruction due to leukemia) or Gilbert's disease
    b. Creatinine clearance >50 ml/min, calculated using the formula of Cockroft and Gault: (140-Age) x Mass (kg) / (72 x Creatinine mg/dL); multiply by 0.85 if female.
    c. Left ventricular ejection fraction of ≥ 40% by MUGA scan or echocardiogram

5. To ensure that no patient will receive a dose of selinexor >70mg/m^2, body surface area (BSA) calculated by Dubois method must be >1.43 m^2

6. 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. It is not anticipated that female patients enrolling in this study will be able to conceive. However, in the rare event that this is possible, female patients 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, effective methods of contraception must be used throughout the study and for three months following the last dose.

7. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Acute promyelocytic leukemia (AML with t(15;17)(q22;q11) and variants).

2. Previous treatment with CLAG or other chemotherapy regimen containing both cladribine and cytarabine.

3. Colony stimulating factors within 2 weeks of study.

4. Active graft versus host disease (GVHD) after allogeneic stem cell transplantation. At least 2 months must have elapsed since completion of an allogeneic stem cell transplantation.

5. Less than 7 days from the completion of any previous cytotoxic chemotherapy (with the exception of hydroxyurea).

6. Concurrent active malignancy under treatment except prostate or breast cancer undergoing treatment with hormonal therapy.

7. Treatment with any investigational agent within three weeks prior to first dose in this study.

8. Active CNS involvement with leukemia.

9. Unstable cardiovascular function:
   a. symptomatic ischemia, or
   b. uncontrolled clinically significant conduction abnormalities (i.e. ventricular tachycardia on antiarrhythmics are excluded and 1st degree AV block or asymptomatic LAFB/RBBB will not be excluded), or
   c. congestive heart failure (CHF) of NYHA class ≥3, or
   d. myocardial infarction (MI) within 3 months

10. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to KPT-330 or other agents used in the study.

11. 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 is acceptable.

12. Any medical condition which, in the investigator's opinion, could compromise the patient's safety.

13. Pregnant and/or breastfeeding. Patient must have a negative urine pregnancy test within 5 days of study entry.

14. Unable to swallow tablets, or diagnosed malabsorption syndrome, or any other disease significantly affecting gastrointestinal function.

15. Known active hepatitis B virus (HBV) or C virus (HCV) infection; or known to be positive for HCV ribonucleic acid (RNA) or HBsAg (HBV surface antigen).

16. Known human immunodeficiency virus (HIV) infection.

17. Serious psychiatric or medical conditions that could interfere with treatment.

3.3 Inclusion of Women and Minorities

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

4 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below

1. Registering physician's name
2. Patient's race, sex, and date of birth
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5 TREATMENT PLAN

5.1 Screen Failures

Patients who sign an informed consent form but do not undergo treatment are defined as screen failures. Screen failures are to be replaced.

5.2 General Considerations

Supportive care for prevention of tumor lysis syndrome (hydration, monitoring, etc.) must be performed per local institutional guidelines. Additional supportive care (e.g. transfusions, prophylactic antibiotics, antifungals and/or antivirals, growth factor support) is also allowed per institutional guidelines.

Co-administration of corticosteroids and corticosteroid-containing eye drops (or equivalent) is recommended for patients receiving cytarabine containing regimens. Eye drops should continue for at least 2 days following the last dose of cytarabine.

Antiemetic prophylaxis given per institutional guidelines is recommended.

Treatment for fatigue and anorexia is recommended for patients receiving selinexor (see guideline Section 5.7)

5.3 Ophthalmic Assessment

A complete ophthalmologic assessment will be conducted on all patients by an ophthalmologist or optometrist. The full ophthalmic assessment includes:

- *Prior to dilation*: best corrected visual acuity and slit lamp examination including tonometry
- *Following dilation*: Fundoscopy and a slit lamp examination to document lens clarity. If a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to a Grade 1-4 system (**Error! Reference source not found.**).

A complete ophthalmic assessment should be performed as clinically indicated during the course of the study to monitor ophthalmic adverse events.

5.4 Overall Treatment Plan

Patients treated with selinexor on Schedule A will receive doses on Days 1, 5, 10 and 12 of a 28 day cycle. Patients treated on Schedule B will be administered selinexor doses on Days 1, 5, 10, 12, 17 and 19 of a 28 day cycle. For patients being treated with selinexor maintenance therapy, selinexor will be administered on Days 1, 8, 15, and 22 of a 28 day cycle. For doses on non-clinic days, patients will be provided doses to take home, one dose per container. Compliance to study medication will be recorded by study personnel after discussion with the patient and drug accountability.

5.4.1 Phase I Dosing

For the Phase I portion, patients will be treated with the following:

Selinexor (S):	Oral doses of 60 mg will be administered
Cladribine (CL):	5 mg/m2/day IV once daily on Days 4-8
G-CSF (G):	300 mcg SC once daily on Days 3-8
Cytarabine (A):	2000 mg/m2/day IV once daily on Days 4-8

Dosing of cladribine and cytarabine should be performed according to actual body weight ± 5% to allow for rounding. Patients will be dosed based on body surface area (BSA) (calculated by Dubois method). Selinexor is dosed on a flat-dosing basis. To ensure that no patient will receive a dose of selinexor >70mg/m^2, body surface area (BSA) calculated by Dubois method must be >1.43 m^2

Schedule A dosing:

Day	1	2	3	4	5	6	7	8	9	10	11	12
	S				S					S		S
			G	G	G	G	G	G				
				A	A	A	A	A				
				CL	CL	CL	CL	CL				
BM			BM									
PB			PB		PB		PB					

Schedule B dosing:

Day	1	2	3	4	5	6	7	8	9	10	11	12	17	19
	S				S					S		S	S	S
			G	G	G	G	G	G						
				A	A	A	A	A						
				CL	CL	CL	CL	CL						
BM			BM											
PB			PB		PB		PB							

5.4.2 Phase II Dosing

The phase II dosing schedule is the most intense schedule in which ≤3 DLTs are observed in 12 patients treated using that schedule. If no DLTs are experienced in Schedule B, then Schedule B will be considered the Phase II dose. The phase I safety analysis together with the conclusion on the recommended dose for Phase II will be distributed to all participating investigators prior to starting the Phase II enrollment.

5.5 Definition of MTD, DLT, Dose Escalation Criteria, and Patient Evaluability

5.5.1 Dose Escalation Criteria

The initial cohort of 6 patients will be dosed according to Schedule A. If no dose limiting toxicities (DLTs) are experienced with the initial cohort of 6 patients treated according to Schedule A, then dosing will be intensified whereby a further cohort of 6 patients will be treated with Schedule B dosing. Six patients will be enrolled in each of two cohorts and an additional cohort of 6 may be added if schedule reduction is indicated. No intracohort dosing schedule intensification is permitted.

Patients who do not receive at least 5 doses of selinexor (either on Schedule A or B) and all doses of CLAG for reasons other than an adverse event at least possibly related to the study treatment will not be considered to have adequate date to support dose schedule escalation and may be replaced at the same dose schedule in the phase I portion of the study.

The decision rule is:

	Schedule A
Number of patients treated	6
Intensify schedule if # of DLT =	0 in 6
Repeat schedule if # of DLT =	1 in 6
Stop if # of DLT =	2 in 6
	Schedule A and B
Accept schedule if # DLTs ≤	3 in 12
De-intensify schedule if # of DLT =	4 in 12 *†
Stop if # of DLT =	5 in 12

* There is no de-escalation below the starting schedule. If 1 DLT is observed in the initial cohort with Schedule A dosing and the Schedule A dosing is repeated in the second cohort, the study will be stopped if 3 DLTs are observed in the second cohort, a total of 4 DLTs in cohorts 1 and 2 together.

† If the schedule is intensified after Schedule A dosing and de-intensification is indicated after schedule B dosing, 6 additional patients will be treated using the

schedule A. Schedule A dosing will be accepted if no more than 2 DLTs are observed in a maximum of 18 patients treated using that schedule.

5.5.2 Dose Limiting Toxicities (DLTs)

DLTs will be defined as any of the following that occur during treatment on Schedule A or B during Cycle 1 that are attributed as possibly, probably, or definitely related to selinexor treatment:

- Grade ≥ 3 nausea/vomiting, dehydration or diarrhea while taking optimal supportive medications
- Grade ≥ 3 fatigue lasting for ≥5 days while taking optimal supportive care and with correction of dehydration, anorexia, anemia, endocrine, or electrolyte abnormalities (See Section 5.5).
- Any other Grade ≥3 non-hematological toxicity except electrolyte abnormalities correctable with supportive therapy
- Grade ≥ 3 AST or ALT elevation lasting longer than 7 days OR Grade ≥ 3 AST or ALT elevation in the setting of bilirubin elevation > 2x ULN (>2X baseline for patients with Gilbert's syndrome)

Patients who have failed to attain hematopoietic recovery by 42 days after the start of therapy should undergo a bone marrow biopsy/aspiration in order to evaluate for prolonged bone marrow aplasia or to document the persistence of leukemia. Prolonged myelosuppression, i.e. marrow cellularity < 5% on Day 42 or later (6 weeks) from start of cycle 1 without any evidence of leukemia, will also be considered in defining DLT.

The following will specifically not be considered DLTs:

- Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm3] lasting ≥7 days;
- Febrile neutropenia (ANC < 1000/mm3 with a single temperature ≥ 38.3ºC or sustained temperature of >38°C for over 1 hour) or
- Grade ≥3 thrombocytopenia with or without associated bleeding

Infection and infection related complications will not be considered DLTs.

Persistent grade 3 or higher neutropenia ≥ 42 days after the start of therapy in the absence of leukemia will be considered a DLT.

In rare instances, an event may fall within the definition of a DLT as defined above but the event may be considered not a DLT (ie: not clinically meaningful/significant). If this occurs, a meeting with all investigators, PI, and possibly the drug manufacturer will take place to thoroughly review the event and supporting data and the reasons for not considering the event a DLT will be clearly documented with supporting rationale. In addition other events may occur which do not meet the definition of a DLT but are concerning to the investigators and sponsor and may be then considered to be DLTs.

5.5.3 Toxicity, Response, and DLT Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment due to treatment related adverse events(s) and have not had any disease assessment.

A patient is evaluable for DLT assessment only during Cycle 1 treatment on schedule A and/or B.

5.6 Selinexor Maintenance Therapy for Patients who Achieve CR/CRi

In both the phase I and II portions of the study, patients are candidates for selinexor maintenance therapy if they have achieved a CR or CRi based on post-treatment bone marrow assessment at the time of hematopoietic recovery and are either (1) transplant ineligible (defined in Section 5.6) or (2) do not have a stem cell transplant donor available. Prior to initiating maintenance therapy with selinexor, a bone marrow biopsy must confirm the presence of the CR or CRi. Maintenance therapy should be initiated no sooner than 30 days, but no more than 90 days following the administration of the last dose of selinexor therapy. Maintenance therapy consists of 60mg selinexor on Days 1, 8, 15, and 22 of a 28 day cycle, continuously until disease relapse, unacceptable toxicity, death, or the institution of additional antileukemic therapy including stem cell transplantation or donor leukocyte infusion.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	S							S						
Day	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
	S							S						

5.7 Assessment of Ineligibility for Stem Cell Transplant

The investigator will perform a comprehensive review of patient characteristics (e.g. age, performance score, organ dysfunctions, co-morbidities) to assess a patient's eligibility for allogeneic stem cell transplant. A detailed description of the reasons for considering a patient ineligible for stem cell transplant will be documented in the source records. If co-morbidities and organ dysfunctions are relevant for considering the patient ineligible for stem cell transplant, the documentation will include the details on organ system, type and stage/grade of dysfunction (e.g. NYHA for heart failure, Child-Pugh for liver cirrhosis, etc.).

5.8 Supportive Care Guidelines

5.8.1 Required Supportive Care Medication

5-HT3 Antagonists
In order to minimize nausea, unless contraindicated, all patients must receive 5-HT3 antagonists (ondansetron 8 mg or equivalent) starting before the first dose of selinexor and continued twice daily (bid) – three times a day (tid) as needed (prn).

5.8.2 Supportive Care Recommendations for Selinexor-Related Adverse Events

Supportive measures for optimal medical care should be provided during participation in this clinical trial. Based on clinical observations in over 450 adult patients treated with selinexor as of 01 October 2014, the main side effects are primarily related to anorexia with poor caloric and fluid intake, fatigue, and nausea. Thrombocytopenia also occurs, although it is rarely associated with bleeding.

Besides the required dexamethasone and 5-HT3, supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers) and other treatments may be administered as described below:

1. Glucocorticoids: In addition to the required dexamethasone supportive care, an additional 4-8 mg dexamethasone (or equivalent glucocorticoid) may be given on the days after selinexor dosing; a maximum of 40 mg dexamethasone or equivalent may be given per week.
2. Appetite stimulants: megestrol acetate at a dose of 80-400 mg daily.
3. Centrally acting agents: per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for anorexia/cachexia and antiemesis [palliative care]) see Appendix 2 (anorexia/cachexia) and Appendix 3 (antiemesis), respectively.
4. NK1R antagonist: aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

Additional information on supportive care and dose modifications for specific adverse events can be found in Supportive Care and Dose Adjustment Guidelines for Non-Hematologic Selinexor-Related Toxicities below

5.8.3 Concomitant Medication and Treatment

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients may continue their baseline medication(s). Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s) and any clinical findings.

5.8.4 Prohibited Medication and Concurrent Therapies

Therapy
Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed. Other investigational agents should not be used during the study. Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor.

Alcohol
Ethanol should be avoided on selinexor dosing days as it may compete for glutathione (GSH)-mediated metabolism.

Medications
Although not prohibited, acetaminophen or acetaminophen-containing products must not exceed a total daily dose of 1 gram on days of selinexor dosing.

Glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products should not be taken during participation in this study as these products may enhance the metabolism of selinexor. Please see Appendix 4 for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

5.9 Prevention of Pregnancy

It is not anticipated that female patients enrolling in this study will be able to conceive. However, in the rare event that this is possible, female patients of childbearing 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, effective methods of contraception must be used throughout the study and for three months following the last dose. If a patient is suspected to be pregnant, selinexor should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing. If a female patient or female partner of a male patient becomes pregnant during therapy or within 3 months after the last dose of selinexor, the investigator must be notified in order to facilitate outcome follow-up.

5.10 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the

protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

Patients will be considered to have completed treatment upon achieving CR, documentation of persistent leukemia, or upon administration of additional antileukemic therapy including stem cell transplantation or donor leukocyte infusion. As documented in Section 5.6, patients who achieve a CR or CRi based on post-treatment bone marrow assessment at the time of hematopoietic recovery and are either transplant ineligible or do not have a stem cell transplant donor available are candidates for selinexor maintenance therapy. Maintenance therapy continues until disease relapse, unacceptable toxicity, death, or the institution of additional antileukemic therapy including stem cell transplantation or donor leukocyte infusion.

5.11 Removal from Study

Patients may be removed from the study for any of the following reasons:

- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.12 Patient Replacement

Patients withdrawn in cycle 1 because of noncompliance not related to study drug related toxicity will be replaced. Patients in the Phase II portion of the trial will not be replaced for any reason

5.13 Duration of Follow-up

Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be followed for a minimum of 30 days post treatment for adverse events. Patients achieving a CR or CRi will be followed for disease progression and/or death every 3 months following completion of treatment until removal from the study, for at least 12 months and up to a maximum of 2 years. For patients being treated with selinexor maintenance therapy, assessments should be performed at least every 2 weeks until removal from study.

6 DOSE DELAYS/DOSE MODIFICATIONS

Toxicity will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03; the therapy modifications described below are applied according to this severity grading.

If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

Each dose modification or treatment delay has to be documented, including the respective reason.

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activities from ~10 mg/m^2 to ≥ 60 mg/m^2. Therefore, in order to optimize specific anti-tumor activity and the patient's tolerability, we will allow for dose and/or schedule modifications as described below. Patients should also be treated aggressively with supportive care to reduce toxicities.

Dose modification pertains to selinexor maintenance therapy only. No dose modification will be permitted in cycle 1 for selinexor or CLAG chemotherapy.

Dose Level	Dose of KPT-330
Dose level 0	60 mg and maintain same schedule
Dose level -1	40 mg and maintain same schedule
Dose level -2	20 mg and maintain same schedule
Dose level -3	Discontinue dosing

Supportive Care and Dose Adjustment Guidelines for Non-Hematologic Selinexor-Related Toxicities

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Fatigue (common)		
Grade 1	Rule out other causes of fatigue. Insure adequate caloric intake and assess volume status. Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 2	Rule out other causes of fatigue. Insure adequate caloric intake and assess volume status. Consider addition 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor. For additional support see NCCN guidelines[36].	Maintain dose. Consult medical monitor for additional option such as temporary dose reduction or short dose interruptions.
Grade 3	See guidelines for Grade 2 fatigue.	Interrupt selinexor dosing until resolved to Grade ≤ 2, For first occurrence of Grade 3, if adequate supportive care resulted in fatigue improving to Grade ≤1 within 7 days, restart selinexor at current dose. Otherwise, restart selinexor at one dose level below (.
Anorexia or Weight loss		
Grade 1	Rule out other causes of anorexia. Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.
Grade 2	Rule out other causes of anorexia. Assess dietary options (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor. Consider megesterol acetate 80-400 mg daily. Consider anabolic steroids such as oxandrolone, or dronabinol (Marinol®) or other cannabinoid, mainly for patients who can't tolerate steroids or at high risk to progress. For additional supportive care see NCCN guidelines[37] (Appendix 2).	Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3	See guidelines for Grade 2 anorexia.	Interrupt dosing with selinexor. Restart selinexor at 1 dose level reduction (once anorexia resolves to Grade ≤ 2 and patient is clinically stable.
Grade 4 (anorexia only)	See guidelines for Grade 2 anorexia.	Stop dosing of selinexor. Restart selinexor at 1 dose level reduction (only if anorexia resolves to Grade ≤ 2, patient is clinically stable other contributing factors have been addressed.
Nausea/ - acute (common)		
Grade 1	Insure adequate caloric intake and assess volume status. Consider alternate 5-HT3 antagonists and/or D2 antagonists as needed. Consider addition of NK1 antagonists. Consider addition of 4-12 mg dexamethasone or equivalent with each dose of selinexor +/- the day after selinexor.	Maintain dose.
Grade 2	See guidelines for Grade 1 nausea. For additional options see NCCN guidelines for antiemesis[38] (Appendix 3).	Selinexor may be skipped intermittently while supportive medications are instituted, usually for <1 week.
Grade 3	See guidelines for Grade 1 nausea. For additional options see NCCN guidelines for antiemesis[38] (Appendix 3).	Interrupt selinexor dosing until resolved to Grade ≤ 2, For first occurrence of Grade 3, if adequate supportive care resulted in nausea improving to Grade ≤1 within 3 days, restart selinexor at current dose. Otherwise, restart selinexor at one dose level below (. If nausea stabilizes for at least 4 weeks at Grade ≤1, then original dose of selinexor may be resumed.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Hyponatremia (common)		
Grade 1 (sodium levels <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). Consider salt supplementation one – two times per day.	Maintain dose.
Grade 3 (sodium levels 126-129nM) without Symptoms	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). Initiate salt supplementation two-three times per day.	Hold selinexor until Grade ≤1 (≥130 nM), restart on the same dose level.
Grade 3 (120-125 nM) or Grade 4 or any Grade 3 with Symptoms	Correct sodium as per institutional guideline. Initiate salt supplementation two-three times per day.	Hold selinexor until resolved to Grade ≤ 1 (≥130nM) then reduce selinexor dose by 1 level (. For Grade 3 hyponatremia, if serum sodium stabilizes to grade ≤1 for at least 4 weeks, then original dose of selinexor may be resumed.
Diarrhea (common)		
Grade 1+2	Diet recommendation as per Benson[39] guidelines. Institute standard anti-diarrheal therapy. After the first occurrence of diarrhea, loperamide 2 mg should be considered prophylactically approximately 1-2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours.	For Grade 2 only, reduce selinexor one dose level (until resolved to ≤ Grade 1, then re-start at the current dose level.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3	Institute IV fluids Diet recommendation as per Benson[39] guidelines. Institute standard anti-diarrheal therapy. Once the symptoms resolve to ≤ Grade 1, loperamide 2 mg should be considered prophylactically approximately 1-2 hours before the administration of selinexor and repeated every 4 hours for the first 12 hours.	Delay selinexor until resolved to ≤ Grade 1, then reduce selinexor dose by one dose level (. If diarrhea stabilizes for at least 4 weeks at Grade ≤1, then original dose of selinexor may be resumed.
Grade 4	Rule out other causes of diarrhea, including infectious agents. In case of opportunistic infection, withdraw all steroids (with tapering if medically appropriate) until culture is negative. Follow institutional guidelines for Grade 4 diarrhea.	Delay selinexor until resolved to ≤ Grade 1, then reduce selinexor dose by one dose level (.
Other selinexor-related adverse events		
Grade 1 or 2	Initiate standard supportive care and follow institutional guidelines.	Maintain dose.
Grade 3	Initiate standard supportive care and follow institutional guidelines.	Delay dose until resolved to Grade ≤ 1 or baseline, then reduce by one dose level (.
Grade 4	Initiate standard supportive care and follow institutional guidelines.	Delay dose until resolved to Grade ≤ 1 or baseline, then reduce by two dose levels (.
All dose modifications should be based on the worst preceding toxicity. * Isolated values of ≥ 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.		

6.2 Conditions not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the above guidelines. Selinexor does not need to be held in the case of electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions.

6.3 Missed or Vomited Doses

6.3.1 Missed Doses

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 hours, then it will be replaced.

Doses should not be administered in less than 36 hours apart and all missed doses should be documented.

6.3.2 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.

7 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.4. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Karyopharm requires that all events be reported as outlined in Section 7.5.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of

Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 7.1.3), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

7.5 Reporting to Karyopharm

In addition to the regulatory and sponsor reporting requirements, the Sponsor (Dr. Geoffrey Uy) will notify Karyopharm in accordance with the Protocol about any and all adverse events (AE), including all non-serious and unexpected AEs every six (6) months in the form of line listing in a format as requested by Company. The Principal Investigator will assess the causal relationship of all AEs to Study Drug and other drugs in the Study in accordance with Section 1.9.2. In addition, any SAE, regardless of the causal relationship to Study Drug occurring after the Subject has signed the Informed Consent Form (as defined below) until thirty (30) days after the Subject has stopped study treatment must be reported to Company within twenty-four (24) hours of Institution and Principal Investigator's awareness on Company's SAE Report Form (a template is provided for this purpose and is attached hereto as Exhibit C). The SAE Report Form will be signed by the Principal Investigator. Any SAE observed after the above-referenced 30-day period should only be reported to Karyopharm if the Principal Investigator suspects that the SAE has causal relationship to the Study Drug.

All notices of adverse events and serious adverse events shall be sent to Karyopharm by email on the appropriate form to the following address:
pharmacovigilance@karyopharm.com

Karyopharm will cross-report applicable suspected unexpected serious adverse reactions (SUSARs) to other investigators and competent authorities and relevant ethics committees in accordance with the FDA's 'Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies' or as per national regulatory requirements in participating countries.

7.6 Classification of Adverse Events by Causality

The Principal Investigator will classify any AE as either Not Related or Related to Study Drug and other drugs in the Study in accordance with the following criteria:

Not related	The lack of a temporal relationship of the event to the study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation
Related	The temporal relationship of the event to the study treatment makes a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

7.7 Other Safety Reporting

The Principal Investigator shall also report all incidences of abuse, misuse, medication errors, overdose, and occupational exposure to Karyopharm on an SAE Report Form, regardless of whether or not there is an associated AE or SAE as soon as possible. In the event the abuse, misuse, medication errors, overdose, and occupational exposure is associated with an SAE, the SAE report form must be submitted within twenty-four (24)

hours of first knowledge of its occurrence. If there is no AE or SAE, the report must be submitted as soon as possible, but in no event later than five (5) business days from the first knowledge of its occurrence. All notices under this section shall be sent to Karyopharm by email to the following address: pharmacovigilance@karyopharm.com.

A new cancer diagnosed during the study (histopathologically different from the cancer under study) is considered and SAE and should be reported to Karyopharm.

Hospitalizations for elective surgery or other medical procedures that are not due to an AE are not considered SAEs. A hospitalization meeting the regulatory definition for 'serious' is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission to the hospital.

Progression of the malignancy (including fatal outcomes) should not be reported as an SAE during the study or within the safety reporting period. Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy, the finding should be reported as an AE or SAE, as appropriate.

Pregnancies must be reported to Karyopharm Pharmacovigilance, regardless of whether the patient withdraws from the study or the study is completed, for 3 months after the patient receives his/her last dose of study treatment. Patients should be instructed to inform the investigator regarding any pregnancies.

7.8 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment or until the start of a subsequent treatment for AML, whichever comes first.

8 PHARMACEUTICAL INFORMATION

8.1 Selinexor (KPT-330)

8.1.1 Supplier

Selinexor tablets will be provided by Karyopharm Therapeutics, Inc at no cost for this study, and will be provided in 20 mg tablets in wallet-sized blister packs (12 tablets per blister pack). Each wallet-size blister package of selinexor tablets will be labeled in accordance with current International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and specific regulatory requirements, e.g., FDA, Health Canada, EMA, etc. Blister packages for take-home use may require additional in-pharmacy labeling with take-home and patient-specific instructions (such as exact dose) depending on country-specific regulations or laws.

The Investigational medicinal product should not be used for any purpose outside the scope of this protocol, nor can Investigational medicinal product be transferred or licensed to any party not participating in the clinical study. Karyopharm's data for Investigational medicinal product are confidential and proprietary and shall be maintained as such by the Investigators.

8.1.2 Dosage Form and Preparation

Selinexor tablets are manufactured 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. The tablets are prepared from a common blend of excipients and all tablet excipients are GRAS (generally regarded as safe) listed and suitable for use in pharmaceuticals.

8.1.3 Storage and Stability

Selinexor tablets will be stored at room or refrigerated temperatures between 5-30°C (41-86°F) in a locked and secured area with restricted access. Room temperature storage is recommended. The tablets should not be stored at freezer temperatures or allowed to freeze. All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

8.1.4 Administration

Selinexor will be administered on schedule A on Days 1, 3, 5, 10 and 12. Patients treated on schedule B will be administered doses on Days 1, 3, 5, 10, 12, 17 and 19. For patients being treated with maintenance selinexor therapy, doses will be administered on Days 1, 8, 15, and 22 of a 28 day cycle.

Each dose will consist of selinexor for oral administration on a fixed dose basis in 20 mg increments. To ensure that no patient will be dosed at a dose >70mg/m2, the study will be limited to patients with a body surface area (BSA) (calculated by Dubois method) >1.43 m^2.

Selinexor will be administered orally at 60mg. Selinexor tablets are to be taken within 30-minutes of solid food consumption together with at least 120 mL (4 ounces) of fluids (water, milk, etc.). Selinexor tablets should not be crushed because of increased risk of dermatologic toxicity if the powder comes in contact with skin.

8.2 Cytosine Arabinoside (AraC, Cytarabine)

8.2.1 Cytosine Arabinoside Description

Chemical Name: 4-amino-1-S-D-arabino-furanosyl-2(1H)-primidinone
Molecular formula: $C_9H_{13}N_3O_5$
Molecular weight: 243.217g/mol
Pharmacologic class: Antimetabolite

8.2.2 Clinical Pharmacology

Cytarabine is metabolized to its active form, cytarabine triphosphate (AraCTP) by deoxycytidine kinase and related kinases. AraCTP serves as an inhibitor of DNA polymerase. AraC also is incorporated into cellular RNA and DNA. It exhibits cell phase specificity, and is active against cells in the S-phase and may also block cells from progressing to S phase from G1.

8.2.3 Pharmacokinetics and Drug Metabolism

After intravenous administration, the disappearance of Cytarabine from plasma is biphasic. There is an initial distributive phase with a half-life of approximately 10 minutes, followed by a second elimination phase with a half-life of approximately 1 to 3 hours. Within 24 hours about 80 percent of the administered drug can be recovered in the urine as the inactive metabolite, AraI. After a single IV administration of Cytarabine, levels in CSF are low. There is little conversion to AraU because of low CSF levels of diaminase.

8.2.4 Supplier

Cytarabine is commercially available and not provided as a study drug and must be supplied by the treating institution.

8.2.5 Dosage Form and Preparation

Cytarabine is supplied as a sterile powder in 100 mg, 500 mg, 1 gram, and 2 gram vials for injection. Cytarabine should be reconstituted with sterile water for injection.

8.2.6 Storage and Stability

Sterile powder should be stored at room temperature 15° -30°C (59°- 86°F). Solutions reconstituted with sterile water without preservative should be used immediately; solutions reconstituted with Bacteriostatic of Water are stable up to 48 hours at room temperature 15° -30°C (59°- 86°F). Solutions with a slight haze should be discarded.

8.2.7 Administration

Cytarabine 2000 mg/m^2/day intravenous infusion once daily over 4 hours on Days 4-8. Dosing should be performed according to actual body weight ± 5% to allow for rounding.

8.3 Cladribine (Leustatin)

8.3.1 Cladribine Description

Chemical Name: 5-(6-amino-2-chloro-purin-9-yl)-2-(hydroxymethyl)oxolan-3-ol
Molecular formula: $C_{10}H_{12}ClN_5O_3$
Molecular weight: 285.687 g/mol
Pharmacologic class: Antimetabolite

8.3.2 Clinical Pharmacology

Cladribine is phosphorylated by deoxycytidine kinase to 2-chloro-2′-deoxy-β-D-adenosine monophosphate (2-CdAMP). 2-CdAMP then accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2′-deoxy-β-D-adenosine triphosphate (2-CdATP). Cells containing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly(ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is also evidence that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis.

8.3.3 Pharmacokinetics and Drug Metabolism

Cladribine plasma concentration after intravenous infusion has been shown to decline multi-exponentially and displays an average half-life of 6.7 +/- 2.5 hours. The volume of distribution is approximately 9L/kg. Cladribine penetrates into CSF, with concentrations reaching approximately 25% of plasma levels. Cladribine is approximately 20% bound to plasma proteins. Little is known regarding the metabolism in human subjects. Limited data has shown that 18% of the administered dose is excreted in the urine of patients treated with a 5-day continuous intravenous infusion. Treatment of patients with renal and hepatic impairment has not been extensively investigated in human subjects.

8.3.4 Supplier

Cladribine is commercially available and not provided as a study drug and must be supplied by the treating institution.

8.3.5 Dosage Form and Preparation

Cladribine is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine as 10 mL filled into a single-use clear flint glass 20 mL vial. Cladribine is supplied in 10 mL (1 mg/mL) single-use vials available in a treatment set (case) of seven vials. Cladribine must be diluted with the designated diluent prior to administration. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agent, aseptic technique and proper environmental precautions must be observed in preparation of the intravenous infusion. The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine.

8.3.6 Storage and Stability

When stored in refrigerated conditions between 2° to 8°C (36° to 46°F) protected from light, unopened vials of cladribine injection are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. DO NOT heat or microwave. Once thawed, the vial of cladribine injection is stable until expiry if refrigerated. DO NOT refreeze. Once diluted, solutions containing cladribine injection should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than 8 hours prior to administration.

8.3.7 Administration

Cladribine 5 mg/m^2/day intravenous infusion once daily over 2 hours on Days 4-8. Dosing should be performed according to actual body weight ± 5% to allow for rounding.

8.4 Filgrastim (G-CSF, Neupogen)

8.4.1 Filgrastim Description

Molecular formula: $C_{845}H_{1339}N_{223}O_{243}S_9$
Molecular weight: 18,800 daltons
Pharmacologic class: Leukocyte growth factor

8.4.2 Clinical Pharmacology

Colony stimulating factors are endogenous lineage specific glycoproteins that acts on hematopoietic cells through binding to a specific cell surface receptor and lead to proliferation, differentiation, and some end-cell functional activation.

G-CSF helps to regulate the production of neutrophils in the bone marrow, and also effects the differentiation and proliferation of neutrophil progenitor cells. G-CSF also plays a role in regulating some end-cell functional activation including

priming cellular metabolism associated with respiratory burst, antibody dependent killing, and enhanced phagocytic ability.

8.4.3 Pharmacokinetics and Drug Metabolism

Absorption and clearance of subcutaneous injection of filgrastim follows first-order pharmacokinetics. The volume of distribution averaged 150ml/kg and the elimination half-life is approximately 3.5 hours.

8.4.4 Supplier

Filgrastim is commercially available and not provided as a study drug and must be supplied by the treating institution.

8.4.5 Dosage Form and Preparation

Filgrastim is commercially available in 1.0 and 1.6 mL vials containing 300 μg and 480 μg G-CSF, respectively.

8.4.6 Storage and Stability

Filgrastim should be stored in the refrigerator at 2° to 8°C (36° to 46°F). DO NOT ALLOW THE DRUG TO FREEZE. Avoid shaking. Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial or prefilled syringe left at room temperature for greater than 24 hours should be discarded.

8.4.7 Administration

Each vial should be entered only once, and the remainder of the vial discarded and not re-entered a second time. 300 mcg once daily on Days 3-8 should be injected subcutaneously in one or two sites.

9 CORRELATIVE STUDIES

9.1 Sample Collection

Ten ml of bone marrow in EDTA tube(s) will be collected at the following time points:

- Screening
- Day 3, prior to the administration of G-CSF
- At the time of hematopoietic recovery

Ten ml of peripheral blood in EDTA tube(s) will be collected at the following time points:

- Screening
- Day 3, prior to the administration of G-CSF
- Day 5, prior to the administration of Selinexor and CLAG chemotherapy
- Day 7, prior to the administration of CLAG chemotherapy
- At the time of hematopoietic recovery

9.2 Sample Handling

All correlative studies will be performed by the DiPersio Lab. Specimens will be transported at room temperature immediately to the DiPersio Lab, Monday through Friday 8AM-5PM. Please notify the lab and/or Dr. DiPersio prior to submission. Sample collections that are outside those hours should be directly discussed with Dr. DiPersio at least 72 hours in advance.

Attention: DiPersio Lab/ Julie Ritchey
WU-Oncology 6th floor, Southwest Tower Building, Room 626
4940 Parkview Place
St Louis, MO, 63110
Lab: (314) 362-9335
jdipersi@DOM.wustl.edu, jritchey@dom.wustl.edu

10 STUDY CALENDAR

Tests & Observations	Baseline Examinations[1]	Treatment Phase[2]	Post-treatment/Maintenance Phase[3]
History	X	C	X
Physical Examination	X	C	X
Performance status	X		
Toxicity assessment	X	A	X
Laboratory Studies			
CBC with differential	X	B	X
BUN, creatinine, electrolytes	X	B	X
Hepatic function tests	X	D	X
LDH, uric acid	X		
MUGA or echocardiogram	X		
Pregnancy test for women of child bearing potential	X		
Bone marrow biopsy/aspiration	X	E	
Ophthalmological exam	G		
Research Studies			
Bone marrow aspirate/biopsy and peripheral blood	F	F	

Notes:

1. All baseline examination are to be performed within 14 days of the start of therapy

2. Treatment phase begins with first dose of selinexor (Day 1) and ends at the time of documentation of CR/CRi or persistent leukemia but no less than 30 days after the start of treatment

3. Assessment for remission status and survival every 3 months until removal from study, for at least 12 months and up to a maximum of 2 years. For patient's being treated with maintenance selinexor therapy, laboratory assessments should be performed at least every 2 weeks with history and physical examination every 4 weeks until removal from study.

A. Performed at least weekly until count recovery

B. Performed daily while inpatient but no less than 15 days and then at least twice a week following discharge until count recovery

C. A symptom directed history and physical should be performed daily while inpatient but no less than 15 days and then weekly after hospital discharge until count recovery

D. Performed at least twice a week while inpatient but no less than 15 days and then at least weekly after discharge until count recovery

E. Performed at the time of hematopoietic recovery to document remission status and/or as clinically indicated to document persistent leukemia. If hematopoietic recovery does not occur prior to Day 42 (6 weeks) then a bone marrow aspirate/biopsy should be attained to evaluate for prolonged bone marrow aplasia. Prior to initiating maintenance therapy with selinexor, a bone marrow biopsy must confirm the presence of the CR or Cri

F. 10 ml of bone marrow aspirate collected in an EDTA containing tube performed at the time of baseline screening marrow, on Day 3 prior to the administration of G-CSF, and at the time of hematopoietic recovery and/or as clinically indicated to document persistent leukemia. 10 ml of peripheral blood collected in an EDTA containing tube performed at baseline, on Day 3 prior to the administration of G-CSF, on Day 5 prior to the administration of Selinexor and CLAG chemotherapy, on Day 7 prior to the administration of CLAG chemotherapy, and at the time of hematopoietic recovery.

G. Full ophthalmological exam will be conducted on all patients by an ophthalmologist or optometrist at baseline visit during Induction phase only, and if clinically indicated during the rest of the study (e.g., monitoring of pre-existing cataracts, visual disturbances). Prior to dilation: assessment of best corrected visual acuity, and slit

lamp examination including tonometry. Following dilation, patients will undergo fundoscopy and a slit lamp examination to document lens clarity. If a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to a Grade 1-4 system (Appendix 5: Cataract Clinical Grading Scale).

11 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form On-Study Labs Form On-Study Correlative Studies Form Cytogenetics and FISH Form Bone Marrow Biopsy Form Molecular Diagnostics Form	Prior to starting treatment
Treatment Form	During treatment
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Bone Marrow Biopsy Form Cytogenetics and FISH Form Response Assessment Form	At time of bone marrow biopsies
Adverse Event Form	Baseline, and at the time of any toxicity
Follow Up Form	Every 3 months
MedWatch Form	See Section 7.0 for reporting requirements

12 MEASUREMENT OF EFFECT

12.1 Disease Parameters

Disease status will be measured by bone marrow aspirate (or biopsy if aspirate is not adequate) at baseline screening and at the time of hematopoietic recovery, and as clinically indicated to assess treatment response.

12.2 Response Criteria

Response to treatment will be assessed according to the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid

Leukemia.[30] All patients who receive at least one dose of selinexor are considered evaluable for response.

Morphologic complete remission (CR): neutrophil count > 1.0 x 10^9 /L, platelet count ≥ 100 x 10^9/L, < 5% bone marrow blasts by morphologic review, no Auer rods, no evidence of extramedullary disease. (No requirements for marrow cellularity, hemoglobin concentration).

Cytogenetic complete remission (CRc): only patients with an identified cytogenetic abnormality may receive this designation. Defined as a morphologic complete remission plus reversion to a normal karyotype (no clonal abnormalities detected in a minimum of 20 mitotic cells).

Morphologic complete remission with incomplete blood count recovery (CRi): same as CR but ANC may be <1000/mcl or platelet count <100,000/mcl

Treatment failure (TF): Treatment failure includes those patients for whom treatment has failed to achieve a CR or CRi and will be classified as below:

a) Treatment failure due to resistant disease includes patients who survive at least 7 days after completion of the final dose of the initial course of treatment but whose last posttreatment peripheral blood smear and/or bone marrow sample showed persistent AML
b) Treatment failure due to complications from aplasia includes patients who survive at least 7 days after the final dose of the initial course of treatment and die while cytopenic, but whose last posttreatment bone marrow was aplastic or hypoplastic, as determined by the institutional morphologist or pathologist, without evidence of leukemia, provided that marrow was obtained within 7 days of death.
c) Treatment failure of indeterminate cause includes three categories of patients:
    i) those who die less than 7 days after conclusion of the initial course of treatment, and
    ii) patients who die 7 or more days after the conclusion of treatment whose most recent peripheral blood smear did not show persistent leukemia and who did not have a bone marrow examination subsequent to therapy
    iii) patients who die without completing the first course of therapy.

Recurrence/morphologic relapse: Defined as reappearance of blasts in the blood or the finding of ≥ 5% blasts in the BM, not attributable to any other cause. New dysplastic changes are considered a relapse. If there are no blasts in the peripheral blood and 5-19% blasts in the BM, the BM biopsy and aspirate should be repeated in > 1 week to confirm relapse.

Response rate (RR): Defined as patients obtaining any response as described above.

Time to neutrophil recovery: Defined as the date of the first dose of study drug to the date that the absolute neutrophil count is >1,000/mm^3

Time to platelet recovery: Defined as the date of the first dose of study drug to the date that the platelet count is >100,000/mm^3 in the absence of platelet transfusions.

Overall survival (OS): Defined as the date of first dose of study drug to the date of death from any cause. OS will be evaluated at 3 month intervals for at least 12 months and up to a maximum of 2 years. .

Event-free survival (EFS): Defined as the interval from the date of first dose of study drug to date of treatment failure including progressive disease, recurrence, or discontinuation for any reason (including toxicity, patient preference, initiation of new treatment without documented progression, or death due to any cause).

Duration of remission (DOR): Defined as the interval from the date complete remission is documented to the date of recurrence.

Relapse-free survival (RFS): For patients achieving a complete remission, defined as the interval from the date of first documentation of a leukemia free state to date of recurrence or death due to any cause.

Allogeneic stem cell transplant utilization: the number of patients proceeding to allogeneic transplant within 2 months following end of study without any additional salvage therapy following study treatment.

13 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual
- Protocol activation date

- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14 STATISTICAL CONSIDERATIONS

14.1 Statistical and Analytical Plans

This is a phase I/II, open label study of selinexor given in combination with CLAG in patients with relapsed/refractory AML.

The phase I portion will use a Bayesian optimal interval design to identify a schedule with grade 3-4 non-hematologic toxicity that does not exceed 20%. Six patients will be enrolled in each of two cohorts and an additional cohort of 6 may be added if schedule reduction is indicated, for a maximum of 24 patients in the Phase I portion. The probability of seeing at least one grade 3-4 non-hematologic toxicity, given a true rate of 20%, is .73 with 6 patients, .93 with 12 patients and .98 with 18 patients. The decision rule is:

	Schedule A
Number of patients treated	6
Intensify schedule if # of DLT =	0 in 6
Repeat schedule if # of DLT =	1 in 6
Stop if # of DLT =	2 in 6
	Schedule A and B
Accept schedule if # DLTs ≤	3 in 12
De-intensify schedule if # of DLT =	4 in 12 *†
Stop if # of DLT =	5 in 12

* There is no de-escalation below the starting schedule. If 1 DLT is observed in the initial cohort with Schedule A dosing and the Schedule A dosing is repeated in the second cohort, the study will be stopped if 3 DLTs are observed in the second cohort, a total of 4 DLTs in cohorts 1 and 2 together.

† If the schedule is intensified after Schedule A dosing and de-intensification is indicated after Schedule B dosing, 6 additional patients will be treated using the Schedule A. Schedule A dosing will be accepted if no more than 2 DLTs are observed in a maximum of 18 patients treated using that schedule.

The phase II portion was designed to compare the primary endpoint of complete remission rate (CR + CRi) with an historical 33%. Patients in the phase I portion of the study, treated at the MTD will count towards the phase II accrual goal for evaluation of the primary endpoint. With a sample size of 40, it will have power of 0.80 at a 0.05 significance level for a two-sided, one-sample test for difference of a proportion from a historical value if the study observes a CR/CRi rate $\geq$ 0.55. A continuous toxicity monitoring rule based on 40 patients will be employed whereby the expected rate of early death or hematologic toxicity is 5% and the maximum allowable rate is 20%. The stopping rule will allow a maximum of 6 cases of excess toxicity in 40 patients (12.5%), and it has at least a 0.88 probability of stopping if the true rate is 20%. The study would be suspended for review if it observed 2 cases in the first 4 patients, or 3 in the first 12 patients, or 4 in the first 21 patients, or 5 in the first 32 patients, or if the 6th case is observed before the 40th patient has completed the study.

Phase I data will be tabulated by patient, type and grade of toxicity. In the phase II portion descriptive statistics will be used to summarize baseline patient characteristics and adverse events by patient, type and severity. Complete remission rate and complete cytogenetic remission rate will be calculated with 95% confidence intervals, as will the proportion of patients able to undergo hematopoietic stem cell transplant. Comparisons with historical rates may be made; if so, one sample tests for difference of proportion will be used. Kaplan Meier estimates will be used to describe the median time to hematologic recovery (neutrophils and platelets), duration of remission, event-free survival, relapse-free survival and overall survival using 95% confidence intervals. The Cox proportional hazard model and logistic regression model will be used to evaluate the association of clinical and laboratory characteristics to survival and response respectively. We will use a P <= 0.05 threshold for significance. Drug-related AEs will be recorded and followed to the end of the study or until resolution. All AEs will be classified using the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and summarized. Exploratory linear and nonlinear mixed models will be used to evaluate correlative endpoints such as bone marrow blast percentage, annexin V/7AAD, and cell cycle status, XPO1 expression, nuclear accumulation of targets such as p53, NPM, Fox03a, IκB in AML blasts, and selinexor concentration. Potential covariates include, but are not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, and concomitant medications.

We anticipate completion of the study in 18-24 months.

15 REFERENCES

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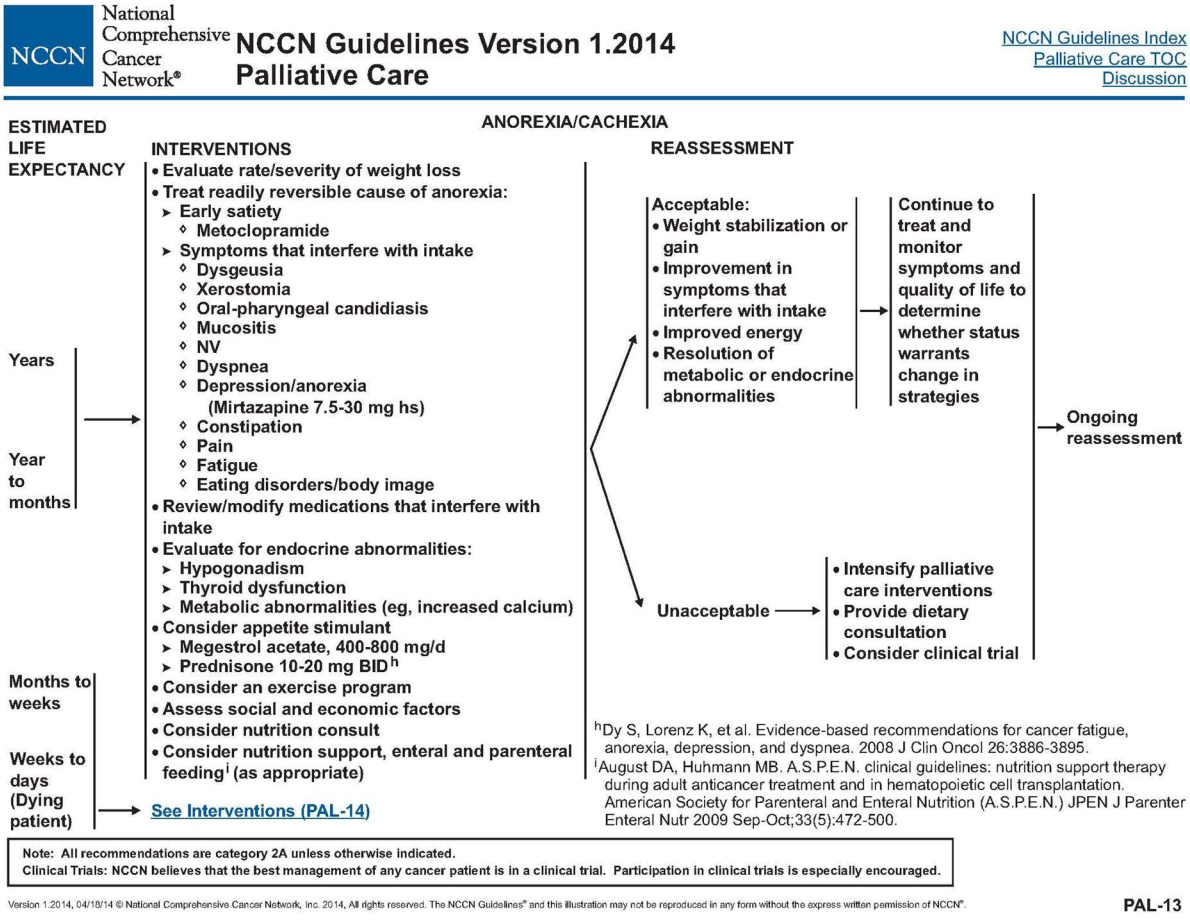
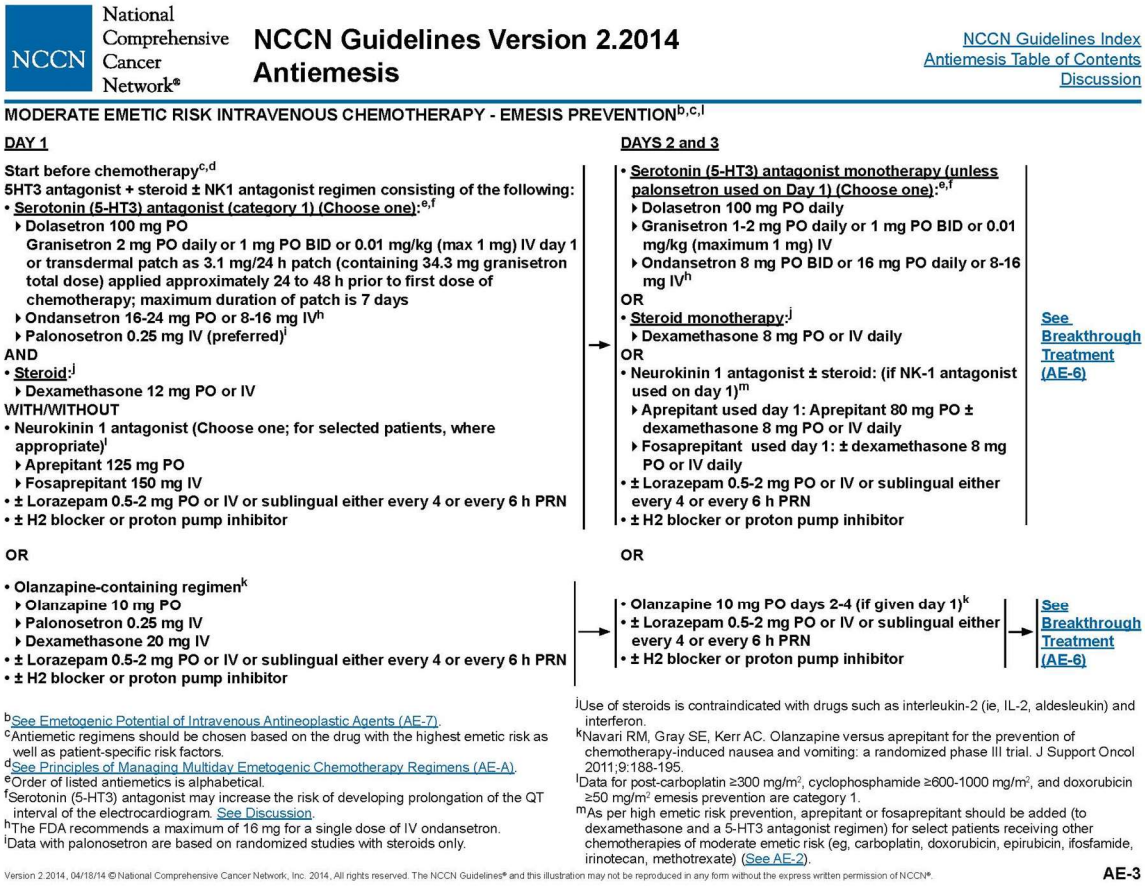
Appendix 1: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 2: NCCN Clinical Practice Guidelines in Oncology: Anorexia/Cachexia



Appendix 3: NCCN Clinical Practice Guidelines in Oncology: Antiemesis



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NCCN Guidelines Version 2.2014
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MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY - EMESIS PREVENTION[b,c,l]

DAY 1

Start before chemotherapy[c,d]
5HT3 antagonist + steroid ± NK1 antagonist regimen consisting of the following:
- **Serotonin (5-HT3) antagonist (category 1) (Choose one):[e,f]**
  - **Dolasetron 100 mg PO**
    Granisetron 2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1 or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24 to 48 h prior to first dose of chemotherapy; maximum duration of patch is 7 days
  - **Ondansetron 16-24 mg PO or 8-16 mg IV[h]**
  - **Palonosetron 0.25 mg IV (preferred)[i]**

AND
- **Steroid:[j]**
  - **Dexamethasone 12 mg PO or IV**

WITH/WITHOUT
- **Neurokinin 1 antagonist (Choose one; for selected patients, where appropriate)[l]**
  - **Aprepitant 125 mg PO**
  - **Fosaprepitant 150 mg IV**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN**
- **± H2 blocker or proton pump inhibitor**

OR

- **Olanzapine-containing regimen[k]**
  - **Olanzapine 10 mg PO**
  - **Palonosetron 0.25 mg IV**
  - **Dexamethasone 20 mg IV**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN**
- **± H2 blocker or proton pump inhibitor**

DAYS 2 and 3

- **Serotonin (5-HT3) antagonist monotherapy (unless palonsetron used on Day 1) (Choose one):[e,f]**
  - **Dolasetron 100 mg PO daily**
  - **Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV**
  - **Ondansetron 8 mg PO BID or 16 mg PO daily or 8-16 mg IV[h]**

OR
- **Steroid monotherapy:[j]**
  - **Dexamethasone 8 mg PO or IV daily**

OR
- **Neurokinin 1 antagonist ± steroid: (if NK-1 antagonist used on day 1)[m]**
  - **Aprepitant used day 1: Aprepitant 80 mg PO ± dexamethasone 8 mg PO or IV daily**
  - **Fosaprepitant used day 1: ± dexamethasone 8 mg PO or IV daily**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN**
- **± H2 blocker or proton pump inhibitor**

See Breakthrough Treatment (AE-6)

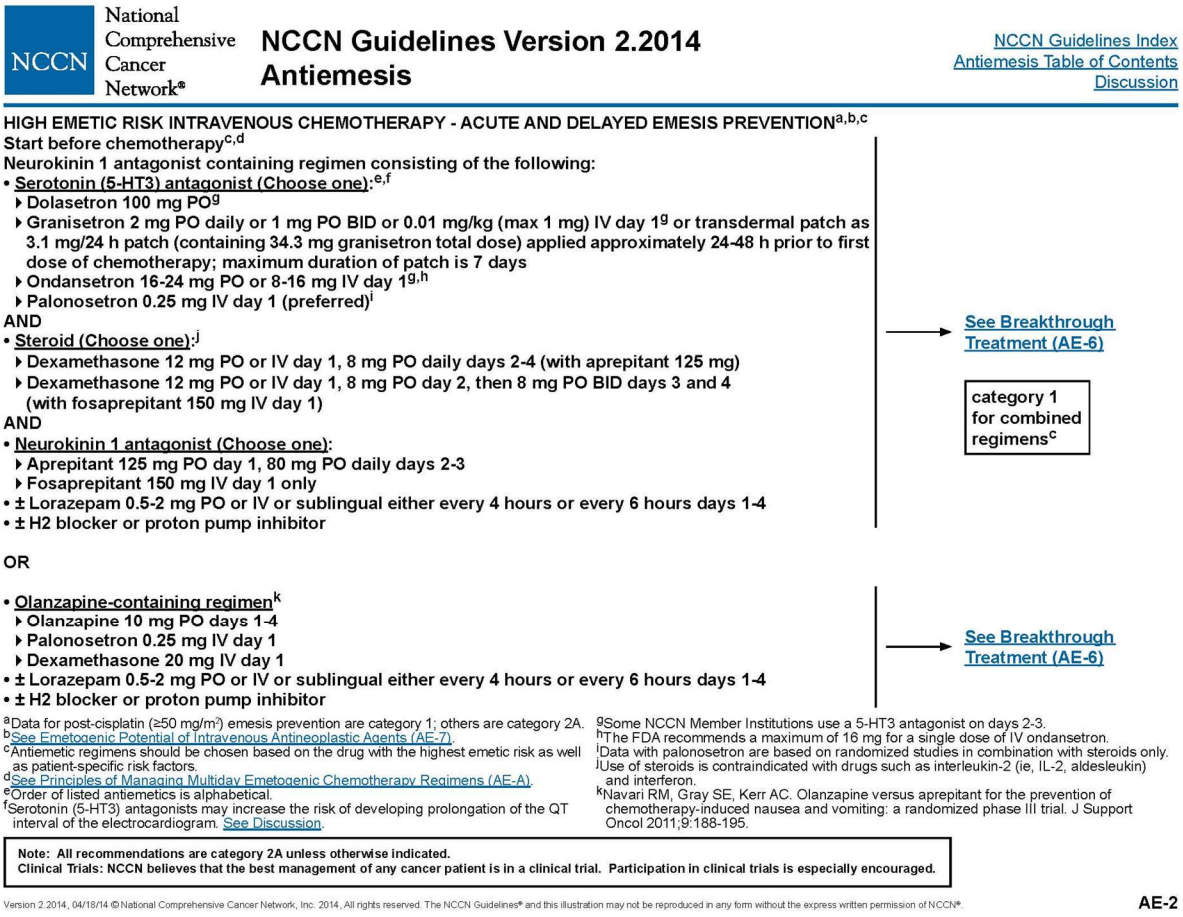
OR

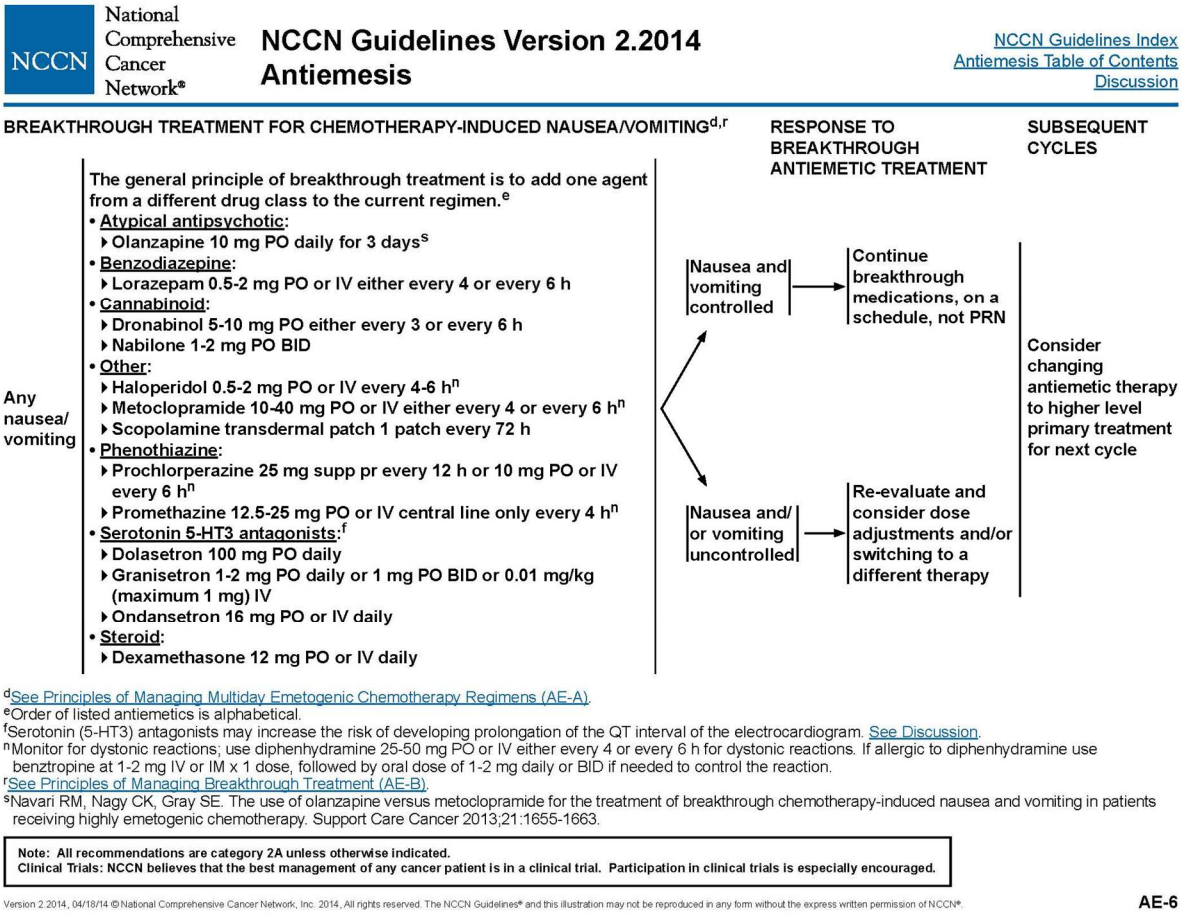
- **Olanzapine 10 mg PO days 2-4 (if given day 1)[k]**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN**
- **± H2 blocker or proton pump inhibitor**

See Breakthrough Treatment (AE-6)

[b] See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-7).
[c] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[d] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[e] Order of listed antiemetics is alphabetical.
[f] Serotonin (5-HT3) antagonist may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.
[h] The FDA recommends a maximum of 16 mg for a single dose of IV ondansetron.
[i] Data with palonosetron are based on randomized studies with steroids only.
[j] Use of steroids is contraindicated with drugs such as interleukin-2 (ie, IL-2, aldesleukin) and interferon.
[k] Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 2011;9:188-195.
[l] Data for post-carboplatin ≥300 mg/m^2, cyclophosphamide ≥600-1000 mg/m^2, and doxorubicin ≥50 mg/m^2 emesis prevention are category 1.
[m] As per high emetic risk prevention, aprepitant or fosaprepitant should be added (to dexamethasone and a 5-HT3 antagonist regimen) for select patients receiving other chemotherapies of moderate emetic risk (eg, carboplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, methotrexate) (See AE-2).

AE-3





Appendix 4: glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products (representative List)

Product Name	Ingredient	Manufacturer/Brand	Strength	Dose Form	Other key ingredients
Glutathione					
Glutathione	glutathione	NOW Foods	500 mg	Vcaps	milk thistle, alpha lipoic acid
Glutathione	L-glutathione	NOW Foods	250 mg	Vcaps	
Glutathione reduced	glutathione	Jarrow Formulas	500 mg	capsules	
Reduced glutathione sublingual complex	glutathione	Source Naturals	50 mg	sublingual	
Glutathione reduced	glutathione	Bulk Supplements	10, 25, 50, 100, 250, 500, 1000 g	powder	
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	Viva Labs	500 mg	capsules	alpha lipoic acid
Glutathione, Cysteine & C	glutathione, 50 mg L-cysteine, 200 mg vitamin C, 500 mg	Life Extension	750 mg	capsules	L-cysteine, vitamin C
Liposomal Glutathione	glutathione	Empirical Labs	4 mL	liquid	
Lypospheric GSH	glutathione	LivOn Laboratories	450 mg	packet	essential phospholipids from soy lecithin
Ivory Caps Skin Enhancement Formula	glutathione	Princeton Nutritional Systems	1500 mg	capsules	
Glutathione GOLD	S-acetyl glutathione	Health Naturally	200 mg	capsules	
Mega-Liposomal Glutathione	glutathione	Aurora NutraScience	750 mg	liquid	
L-Glutathione 500	L-glutathione	GNC	500 mg	capsules	
N-acetylcysteine (NAC)					
Acetadote for acetaminophen overdose	acetylecysteine	Cumberland Pharmaceutcals	IV	sterile solution, 200 mg/mL	
CerefolinNAC medical food for age-related memory loss	L-methylfolate vitamin B12 N-acetyl cysteine	PAMLAB, LLC	600 mg NAC	caplets	L-methylfolate vitamin B12
NAC	N-acetyl cysteine	NOW Foods	600 mg	capsules	selenium, molybdenum
N-A-C Sustain	N-acetyl L-cysteine	Jarrow Formulas	600 mg	capsules	
Best NAC Detox Regulators	N-acetyl cysteine	Doctor's Best	600 mg	capsules	selenium, 50 mg molybdenum, 50 mg
S-adenosylmethionine (SAM)					
SAM-e Complete	S-adenosylmethionine	Nature Made	400 mg	tablets	

SAMe	S-adenosyl-L-methionine	NOW Foods	400 mg	tablets	
Double Strength SAMe 400	S-adenosylmethionine	Doctor's Best	400 mg	tablets	
SAM-e 200	S-adenosylmethionine	Jarrow Formulas	200 mg	tablets	
SAMe	S-adenosyl-l-methionine	Source Naturals	400 mg	tablets	
SAMe	S-adenosyl-l-methionine	Source Naturals	200 mg	tablets	
SAMe	S-adenosylmethionine	Natrol	400 mg	enteric coated tablets	
SAMe	S-adenosyl-methionine	NOW Foods	200 mg	tablets	vitamin B-6, folic acid, vitamin B-12

Appendix 5: Cataract Clinical Grading Scale

Grading of Cataracts*				
Cataract Type	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Nuclear Yellowing and sclerosis of the lens nucleus	Mild	Moderate	Pronounced	Severe
Cortical Measured as aggregate percentage of the intrapupillary space occupied by the opacity	Obscures 10% of intrapupillary space	Obscures 10% -50% of intra-pupillary space	Obscures 50% -90% of intra-pupillary space	Obscures >90% of intrapupillary space
Posterior subcapsular Measured as the aggregate percentage of the posterior capsular area occupied by the opacitiy	Obscures 10% of the area of the posterior capsule	Obscures 30% of the area of the posterior capsule	Obscures 50% of the area of the posterior capsule	Obscures >50% of the area of the posterior capsule
*Designation of cataract severity that falls between grade levels can be made by addition of a + sign (e.g., 1+, 2+). Grading of cataracts is usually done when pupil is dilated.				

Modified from Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataracts: available on the American Optometric Association website: www.aoa.org