CLINICAL STUDY PROTOCOL

KCP-330-008

A RANDOMIZED, OPEN LABEL, PHASE 2 STUDY OF THE SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE) SELINEXOR (KPT-330) VERSUS SPECIFIED PHYSICIAN'S CHOICE IN PATIENTS ≥ 60 YEARS OLD WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA (AML) WHO ARE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY AND/OR TRANSPLANTATION

SOPRA Study: Selinexor (KPT-330) in Older Patients with Relapsed AML

Drug Development Phase:	Phase 2
Investigational Product:	Selinexor (KPT-330)
Indication:	Acute Myeloid Leukemia
EudraCT Number:	2014-000920-26
Sponsor:	Karyopharm Therapeutics, Inc. 85 Wells Avenue Newton, MA 02459 USA
Protocol Date and Version:	21 January 2014, Version 1.0 03 July 2014, Version 2.0 (Amendment 1) 30 September 2014, Version 2.1 (United Kingdom-specific Amendment 2) 25 November 2014, Version 3.0 (Amendment 3) 24 April 2015, Version 4.0 (Amendment 4) 09 July 2015, Version 4.1 (Germany-specific Amendment 4.1) 04 August 2015, Version 5.0 (Amendment 5)

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

PROTOCOL VERSION 5.0 APPROVAL SIGNATURE PAGE

SPONSOR: KARYOPHARM THERAPEUTICS, INC.

I have read and understand the contents of this clinical protocol Version 5.0 for Study No. KCP-330-008 dated 04 August 2015 and agree to meet all obligations of Karyopharm Therapeutics, Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

PPI

PPI

Karyopharm Therapeutics Inc.

PPI

Date PPI

PPI

Karyopharm Therapeutics Inc.

PPI

Date PPI

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol Version 5.0 for Study No. KCP-330-008 dated 04 August 2015 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices, ICH E6 and applicable FDA regulatory requirements:

Name of Principal Investigator:

Principal Investigator's Signature: _____

Principal Investigator's Name: _____

Institution: _____

Date: _____

PROTOCOL SYNOPSIS

Sponsor: Karyopharm Therapeutics, Inc.	**Investigational Product:** Selinexor (KPT-330)	**Developmental Phase:** Phase 2

Title of Study: **SOPRA (Selinexor in Older Patients with Relapsed AML)**: A Randomized, Open Label, Phase 2 Study of the Selective Inhibitor of Nuclear Export (SINE) **Selinexor** (KPT-330) versus Specified Physician's Choice in Patients ≥ 60 Years Old with Relapsed/Refractory Acute Myeloid Leukemia (**AML**) Who are Ineligible for Intensive Chemotherapy and/or Transplantation

Protocol Number: KCP-330-008

Indication: Acute Myeloid Leukemia (AML)

Objectives:

Primary Objective:

To determine overall survival (OS) of selinexor as compared to physician's choice (PC) in patients ≥ 60 years old with relapsed/refractory AML that requires treatment and are ineligible for intensive chemotherapy and/or transplantation.

Secondary Objectives:

- To determine the proportion of patients whose OS is at least 3 months (OS3.0)
- To determine the complete remission rate (CRR), including complete remission with full hematologic recovery (CR), and median disease free survival (DFS) for patients who achieve CR
- To determine the modified CRR (mCRR), including CR or complete remission with incomplete hematologic recovery (CRi) (including complete remission with incomplete platelet recovery [CRp]), and median DFS for patients who achieve CR or CRi (including CRp)
- To determine the overall response rate (ORR) and duration of overall response (DOR), including CR, CRi, morphologic leukemia-free state (MLFS), and partial remission (PR)
- To determine the disease control rate (DCR) defined as ORR + stable disease for ≥ 4 weeks (SD), and duration of DCR
- To assess the safety and tolerability of selinexor (KPT-330), as compared to physician's choice (PC)
- Quality of life and patient reported outcomes (FACT-Leukemia, EQ-5D-5L) (QoL)

Methodology:

This is a randomized, multicenter, open-label, Phase 2 study of the Selective Inhibitor of Nuclear Export (SINE) compound selinexor given orally versus specified investigator choices (one of three potential salvage therapies).

Approximately 300 patients will be randomized into the selinexor or PC treatment arms in a 2:1 allocation, with a 2:1 allocation performed within each of the 2 x 2 x 2 stratification levels. Two separate cohorts will be randomized. Under Protocol Versions < 5.0, approximately 110 patients were randomized to selinexor at a fixed dose of ~55 mg/m^2 versus PC as of

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04 August 2015; enrollment will continue until Protocol Version 5.0 is approved. Approximately 171 additional patients will be randomized under Protocol Versions ≥ 5.0, to either 60 mg of selinexor (flat dose) or PC, again in a 2:1 randomization allocation within strata. Patients will be stratified for randomization using three criteria: (1) duration of their first CR on prior therapy, > 6 months versus ≤ 6 months or never achieved CR; (2) number of prior therapies, 1 versus >1; (3) peripheral leukemic blast counts ≥ 10,000/μL versus < 10,000/μL.

Diagnosis and Main Criteria for Inclusion:

Patients age ≥ 60 years with relapsed/refractory AML (defined using WHO criteria) of any type except for acute promyelocytic leukemia (APL; AML M3), who have poor prognosis (intermediate or adverse risk) cytogenetics, with relapsed or refractory AML, after at least one prior AML therapy (must have included an adequate trial of a hypomethylating agent with at least 2 cycles), who have never undergone, and who are not currently eligible for stem cell transplantation, and are currently deemed unfit for intensive chemotherapy.

Main Criteria for Exclusion:

Patients with AML M3, known central nervous system (CNS) leukemia, who are in blast transformation of chronic myeloid leukemia (CML), or whose AML is classified as favorable according to the European LeukemiaNet (ELN) disease risk assessment will be excluded from this study.

Test Product, Dose and Mode of Administration:

Selinexor (KPT-330) will be given initially at an oral fixed dose of 60 mg (equivalent to ~35 mg/m^2) twice weekly (e.g., Monday and Wednesday or Tuesday and Thursday or Wednesday and Friday). Patients who were randomized to selinexor (~55 mg/m^2) under protocol versions < 5.0 will be switched to the 60 mg fixed dose. The dose has been reduced in response to a possible increase in sepsis related serious adverse events for selinexor ~55 mg/m^2 (8 sepsis events) versus PC (2 sepsis events) (a ratio of 4:1 and not the expected 2:1) that was detected during an annual review of clinical safety data (29 July 2015).

Reference Therapy, Dose and Mode of Administration: One of the following three best supportive care (BSC) regimens will be selected by the treating physician / investigator (physician's choice [PC]): (1) BSC including blood product transfusions, antimicrobials, growth factors as needed, and hydroxyurea; or (2) BSC + low dose AraC, 20 mg bid by subcutaneous (sc) injection daily on Days 1-10/14 (20/28 doses) to be repeated at 28 to 42 day intervals; or (3) BSC + hypomethylating agent: azacitidine 75 mg/m^2 by sc injection daily on Days 1-7 or 1-5 and 8-9 (7 doses) to be repeated at ≥28 day intervals, *or* decitabine (20 mg/m^2 IV over 1 hour daily on days 1-5 or days 1-10 to be repeated at ≥ 28 day intervals).

Sponsor:	**Investigational Product:**	**Developmental Phase:**
Karyopharm Therapeutics, Inc.	Selinexor (KPT-330)	Phase 2

Supportive Care and Concomitant Medications:

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). In addition, aggressive use of other supportive care including anti-nausea/anti-emetic therapy, appetite stimulants, acid suppression (proton pump inhibitors and/or H2-blockers) and other treatments is strongly recommended

Patients may continue their baseline medication(s). Patients will receive concomitant medications to treat symptoms, AEs, and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed. Patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Glucocorticoids ≤ 10 mg oral prednisone (or equivalent) per day are permitted at baseline and during the study for non-malignant conditions (i.e., asthma, irritable bowel disease [IBD], etc.) as needed but patients should preferably have been on a stable dose for at least two weeks before study entry. Acetaminophen on days of selinexor dosing will not exceed a total daily dose of 1 gram.

Concurrent therapy with glucocorticoids and hydroxyurea as specified herein is allowed in both arms. Hydroxyurea may be used at any time during the study, typically in patients with WBC ≥ 30,000/μL or per institutional guidelines. Prior to the initiation of hydroxyurea please consider the contraindications in the Summary of Product Characteristics (SPC), including leukocytopenia (< 2.5 x 10^9 leukocytes/L), thrombocytopenia (< 100 x 10^9 platelets/L) or severe anemia.

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

Study Duration:

The treatment period for an individual patient is expected to be up to 6 months, but there is no maximum treatment duration. Treatment may continue until:

- Disease progression defined as an increase in blast counts and absence of hematologic recovery (one or more lineages)
- Unacceptable AEs
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol

Patients will be followed for survival until the last patient has been followed for 6 months from the end of treatment, disease progression, another withdrawal criterion is met, or until death, whichever comes first.

Criteria for Evaluation:

Safety:

The safety and tolerability of selinexor and PC will be evaluated by means of AE reports, physical examinations, and laboratory safety evaluations. The Common Terminology Criteria for Adverse Events (CTCAE) V4.03 will be used for grading of AEs. Investigators will provide their assessment of causality for all AEs as 1) unrelated, 2) possibly related, or 3) related.

Efficacy:

Overall survival (OS) is the primary efficacy variable for the study, where OS is measured from date of randomization to study drug (selinexor or PC) until date of death from any cause. The analysis of OS will be performed on the intent-to-treat (ITT) population as the primary analysis, and on the per-protocol (PP) population as a supportive analysis.

Secondary efficacy variables will include the following, assessed in hierarchical fashion in the order presented, according to the definitions presented above (Secondary Objectives):

- OS3.0
- CRR and DFS for CRR
- mCRR and DFS for mCRR
- ORR and DOR
- DCR and duration of DCR
- Quality of Life (QoL)

Disease response assessment will be made according to the International Working Group (IWG) criteria (Cheson 2003). Response assessments (CRR, mCRR, ORR, DCR) will be assessed for treatment arm differences in rates of response, followed by assessment of differences in duration of response.

Criteria for Treatment Discontinuation:

At the discretion of the investigator, the investigator may remove a patient from study treatment for the following reasons:

- Disease progression defined as an increase in blast counts and absence of hematologic recovery (one or more lineages)
- Unacceptable AEs or failure to tolerate the study treatment
- Patient decides to discontinue study therapy
- Significant deviation from entry criteria (e.g., non-relapsed or non-refractory AML)
- Misuse of study medication (e.g., deliberate overdosing by patient)
- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk
- Any other medically appropriate reason or significant protocol violation in the opinion of the investigator.

Patients may decide to discontinue study treatment for any reason. Patients who elect not to initiate study treatment or to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be

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obtained. However, patients may elect to withdraw consent and decline further participation in the trial.

Statistical Methods:

Patients enrolled under Protocol Versions < 5.0 will not be included in the efficacy analyses due to changes to the selinexor dose and the inclusion criteria. Therefore, sample size justification refers to patients enrolled under Protocol Versions ≥ 5.0. The sample size is designed to have 80% power to detect an improvement in the median OS with selinexor of ~5.2 months, versus investigator choice of ~3.0 months, using a one-sided alpha of 0.025, with a 2:1 allocation of treatment to selinexor:PC, and allowing for two interim analyses. A total of 123 events (deaths) are required for the primary analysis. The follow up period for survival is up to 6 months after the end of treatment for the last enrolled patient for the primary analysis, and an ~20% drop out rate is assumed.

Two interim efficacy analyses will be conducted. The first interim analysis will take place after 31 (25%) OS events have occurred, and will be conducted to assess futility only (non-binding). Futility would be concluded if the p-value from the log-rank test is ≥ 0.8084. The second interim analysis will take place after 62 (50%) deaths, and will allow for a conclusion of significant efficacy at an α-level < 0.0015, and stopping for futility (non-binding) at an α-level ≥ 0.2879. The final hypothesis test will be performed after 123 OS events are observed with a one-sided significance level of 0.0245. Type I error adjustments will be made using the O'Brien-Fleming approach.

The intent-to-treat population (ITT) will consist of all patients who are randomized to study therapy under Protocol Versions ≥ 5.0. This population will be used for primary analyses of efficacy. An additional, per-protocol population will consist of all patients randomized under Protocol Versions ≥ 5.0 who receive at least one dose of study medication, have post-baseline efficacy follow-up information and are otherwise compliant with all critical protocol requirements, as determined by blinded review of protocol violations prior to study completion.

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals, unless otherwise stated. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

The stratified log-rank test will be used to test the null hypothesis that the OS distributions are the same for both treatment groups versus the alternative hypothesis that the duration of OS for the selinexor + BSC treatment arm is longer than the group treated with PC. Stratification factors in this analysis are those that were used for randomization. The hazard ratio for treatment group will be estimated from a stratified Cox proportional hazards model (stratified

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by randomization strata). The adequacy of the model will be evaluated, including an assessment of the proportional hazards assumption. CCI [redacted]

The analysis of the difference between treatment arms in the proportion of patients with OS3.0 will be based on the Kaplan-Meier analysis. The analysis of CRR, mCRR, ORR and DCR will be performed using the Cochran-Mantel-Haenszel statistic, stratified by the randomization strata. The analysis of duration of response for each response type (DFS, ORR and DCR duration) will be performed using the same time to event methodology as used for OS.

Safety analysis will be performed on all patients who receive at least one dose of study treatment, based on the treatment actually received, regardless of which protocol version they were enrolled under. The incidence rates of selected treatment-emergent AEs, serious AEs, AEs of at least Grade 3 in severity, related AEs, and AEs leading to withdrawal of treatment may be analyzed for treatment group differences using Fisher's Exact test. Treatment-emergent AEs will be those that start or worsen on or after the first day of study treatment, through 30 days after last dose; related AEs will be those with an investigator determination of related to treatment. Laboratory data will be analyzed by summary statistics over time, as well as by shift tables based on CTCAE V4.03 grades of severity.

Table 1: Schedule of Assessments and Study Activities

	Screening		Cycle 1 (28 days per cycle)	Cycles 1-3	Cycles 2-5		Cycle ≥ 6 (28 days per cycle)	Final Visit	30 Day Safety Follow-up[27]	Survival Follow-up[28]
					Cycles 2-5 (28 days per cycle)	Cycle 2 only (28 days per cycle)				
	Within 14 days prior to start of therapy	Within 7 days prior to start of therapy	Day 1 of each week	Day 4 of each week[25]	Days 1 & Day 15	Days 8 & Day 22	Day 1	≤ 30 days after last dose		
Visit window [days]			± 1 day	+ 1 day	± 2 days	± 2 days	± 2 days	± 7 days	± 7 days	
Study Visit Number	Visit 1	Visit 2	Visits 3, 5, 6, 7	Visit 4 (C1D4) /Weekly Phone Call	Visits 8, 10, 12-17	Visits 9 & 11	Visits 18+	In Clinic	Clinic or Phone	Phone
Informed consent[1]	X									
Inclusion and exclusion criteria		X								
Demographics	X									
Medical History[2]	X									
Randomization[3]			X[3]							
Body height and weight[4]		X	X		X		X	X		
BSA[5]		X	X		X		X			
Vital signs[6]		X	X		X	X	X	X		
Physical examination and ECOG[7]		X	X		X		X	X		
Baseline Symptoms	X	X								
Disease risk assessment (Visit 1 or 2)	X									
Ophthalmic exam[8]	X							X		
Oxygen saturation[9]		X	X		X		X	X		
12-lead ECG[10]	X		X		X		X	X		
Urine analysis[11]		X	X		X		X	X		
Hematology (CBC with differential)[12]		X	X		X	X[26]	X	X		
Complete Serum chemistry[13]		X	X			X[26]		X		
Limited Serum chemistry[14]					X		X			
Coagulation test (PT, PTT or TT) [15]		X	X		X		X			

	Screening		Cycle 1 (28 days per cycle)	Cycles 1-3	Cycles 2-5		Cycle ≥ 6 (28 days per cycle)	Final Visit	30 Day Safety Follow-up[27]	Survival Follow-up[28]
					Cycles 2-5 (28 days per cycle)	Cycle 2 only (28 days per cycle)				
	Within 14 days prior to start of therapy	Within 7 days prior to start of therapy	Day 1 of each week	Day 4 of each week[25]	Days 1 & Day 15	Days 8 & Day 22	Day 1	≤ 30 days after last dose		
Visit window [days]			± 1 day	+ 1 day	± 2 days	± 2 days	± 2 days	± 7 days	± 7 days	
Study Visit Number	Visit 1	Visit 2	Visits 3, 5, 6, 7	Visit 4 (C1D4) /Weekly Phone Call	Visits 8, 10, 12-17	Visits 9 & 11	Visits 18+	In Clinic	Clinic or Phone	Phone
Bone marrow aspirate (assessment of disease status and correlative studies)[16]		X (8-14 days prior to 1st dose if approved by sponsor[16])			X (Day 1 Cycle 2 and as clinically indicated)		X (if clinically indicated)			
Chest radiograph[17]	X									
Selinexor dosing in clinic[18]			X		X	X	X			
Blood draws for pharmacokinetic (PK) testing[19]			X		X		X			
CCI										
Blood draw for correlative studies using peripheral blasts[21]		X			X					
FACT-Leu and EQ-5D-5L QoL questionnaires[22]			X (Week 1 only)		X (Day 1 only)		X	X		
Nutritional Consultation[23]			X							
Review of temperature diary[24]			X (Weeks 2-4 only)	X	X	X	X	X		
Adverse events			X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X		

	Screening		Cycle 1 (28 days per cycle)	Cycles 1-3	Cycles 2-5		Cycle ≥ 6 (28 days per cycle)	Final Visit	30 Day Safety Follow-up[27]	Survival Follow-up[28]
					Cycles 2-5 (28 days per cycle)	Cycle 2 only (28 days per cycle)				
	Within 14 days prior to start of therapy	Within 7 days prior to start of therapy	Day 1 of each week	Day 4 of each week[25]	Days 1 & Day 15	Days 8 & Day 22	Day 1	≤ 30 days after last dose		
Visit window [days]			± 1 day	+ 1 day	± 2 days	± 2 days	± 2 days	± 7 days	± 7 days	
Study Visit Number	Visit 1	Visit 2	Visits 3, 5, 6, 7	Visit 4 (C1D4) /Weekly Phone Call	Visits 8, 10, 12-17	Visits 9 & 11	Visits 18+	In Clinic	Clinic or Phone	Phone
Collect information regarding antineoplastic therapy after end of selinexor or PC treatment								X	X	X

BSA = Body Surface Area; ECOG = Eastern Cooperative Oncology Group; PT = Prothrombin Time; PTT = Partial Thromboplastin Time; FACT-Leu = Functional Assessment of Cancer Therapy - Leukemia; QoL = Quality of Life.

[1] Prior to the first study-specific measures
[2] Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.
[3]Randomization must occur ≤ 3 calendar days of Cycle 1 Day 1.
[4] Body height will be measured at screening only
[5] Body Surface Area (BSA) calculated by Dubois (Dubois and Dubois, 1916) or Mosteller (Mosteller 1987) method
[6] Vital signs: blood pressure, pulse and temperature
[7] Full physical examination for baseline and end of study visit. Physical examinations during the study should be symptom-directed.
[8] Full ophthalmic examination will be conducted on all patients by an optometrist or ophthalmologist at screening, as clinically indicated during the study and at the Final Visit. 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 exam to document lens clarity. If a cataract is seen during the examination for newly enrolling patients or enrolled patients for whom no cataracts have been detected to date, the cataract will be graded using a Grade 1-4 scale (Appendix 3). However, patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the Grade 1-4 scale.

[9] Pulse oximetry is performed for patients at rest breathing room air.
[10] ECG on Day 1 of each cycle only
[11] Urine analyses will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

[12] Hematology: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.

[13] Complete Serum Chemistry for baseline, Cycle 1 Weeks 1, 2, 3, and 4 and Final Study Visit includes Sodium, Potassium, Chloride, Bicarbonate, Blood Urea Nitrogen (BUN) or Urea, Creatinine, and Glucose, Calcium, Phosphate, Magnesium, Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase, Total Bilirubin, Lactic Dehydrogenase (LDH), Total Protein, Albumin, Pancreatic Amylase, Lipase, Creatine Kinase, Thyroid-Stimulating Hormone (TSH), and Uric Acid.

[14] Limited Serum Chemistry for Days 1 and 15 of Cycles 2 through 5 and Day 1 of Cycle ≥6 including Sodium, Potassium, Chloride, Bicarbonate, BUN or Urea, Creatinine, Glucose, ALT, AST, Alkaline Phosphatase, Total Bilirubin, Thyroid-stimulating Hormone (TSH), and LDH.

[15] Coagulation test includes prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT). Coagulation may also be measured using thromboplastin time (Quick test) if measurement of PT/PTT is not feasible.

[16] Disease status will be measured by bone marrow aspirate (or biopsy if aspirate is not adequate) at Screening and on Day 1 of Cycle 2, and as clinically indicated to assess treatment response. In certain cases, a bone marrow aspirate/biopsy may be taken up to 14 days of Day 1 of Cycle 1 after consultation with, and approval by, the sponsor. A portion of the bone marrow aspirate at Screening and Cycle 2 Day 1 will be used for correlative studies to include immunophenotyping, cytogenetic and molecular analysis (FLT3 ITD or TKD mutation or NPM1 mutations). If the patient has achieved CR, Bone Marrow (BM) aspiration/ biopsies are not required unless clinically indicated. For patients with circulating blasts in peripheral blood, there is no need to perform the BM aspirates and biopsies for Cycles >2. For patients without circulating blasts that achieved a PR or SD, BM aspiration/ biopsies will be conducted every other cycle until CR/CRi is achieved, or until progression.

[17] Both posteroanterior and lateral films should be obtained for baseline. Note: this test does not need to be repeated if results are available from a test performed 30 days prior to start of therapy. This test serves as a baseline in the event that patients develop any AEs during the study.

[18] Dosing on Day 1 and 3 of each week of four-week cycle. For doses on non-clinic days, patient will be provided doses to take home, one dose per container.

[19] PK sampling for patients in selinexor arm only. Blood draws (2 mL) for PK analysis will be performed at the following times relative to in-clinic selinexor dose:

- CYCLE 1
  - Day 1: 0 (predose), 1, 2, and 4* hours post-dose (± 10 min for each time point)
  - Day 8: 0 (predose) and 1 hour post-dose (± 10 min)
  - Day 15: 0 (predose) and 1 hour post-dose (± 10 min)
  - Day 22: 0 (predose) and 1 hour post-dose (± 10 min)
- CYCLE ≥ 2
  - Day 1: 0 (predose), 1, and 2* hours post-dose (± 10 min for each time point)

*If possible, an additional blood sample will be collected just prior to patient discharge from the clinic on Day 1 of Cycles 1 – 5, provided discharge time is at least 1 hour after collection of the previous sample. This sample will be labeled "pre-discharge Day 1;" the time of blood collection will be recorded in the study data.

If a clinic visit to include PK sampling occurs on a non-dosing day, PK sampling for that visit will not be done.

[20] CCI [redacted]

[21] Blood draws for correlative studies using will be collected from all patients. 2 x 2.5 mL will be collected during Screening and on Day 1 of Cycle 2 only. For patients in selinexor group, blood should be collected pre-selinexor dose.

[22] Quality of Life (FACT-Leu and EQ-5D-5L) questionnaires will be completed on Day 1 of each treatment cycle and the Final Visit **BEFORE** they undergo any treatment related procedures including study treatment administration.

[23] Selinexor Patients ONLY- It is strongly recommended that patients be given nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor.

[24] Patient is to take their temperature each morning and record their temperature on the diary card that has been provided. The temperature diary will be reviewed with site personnel during each site visit or phone call.
[25] A visit (Visit 4) at Cycle 1 Day 4 (+1 day) is required to monitor adverse events (including infections), to review temperature diaries, to evaluate supportive care medications, and to adjust supportive care as appropriate. Weekly phone calls to the patient may be done in place of visits at Day 4 (+1 day) for all other weeks during Cycles 1-3.
[26] Hematology and complete serum chemistry will be done only if fever and suspected infection are present.
[27] By phone (or a visit, if possible), assess overall medical condition of the patient and status of his/her AML, follow-up on any AEs that were not resolved at the Final Study Visit, and information on any antineoplastic therapies utilized since discontinuation of study treatment.
[28] After treatment discontinuation, a call will be made to the patient (or the patient's family) every 3 months until the End of Study (Section 11.3) to inquire about the patient's AML status, well-being, and information on any antineoplastic therapies utilized since discontinuation of study treatment.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase (SGPT)
AML	Acute Myeloid Leukemia
AML M3	acute promyelocytic leukemia
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
AR	adverse risk
AraC	cytosine arabinoside
AST	aspartate transaminase (SGOT)
AUC_{last}	Area under the Curve, first-last measurement
AV	atrioventricular
bid	twice daily
BM	bone marrow
BMI	body mass index
BMSC	bone marrow stroma cells
BP	blood pressure
BSA	body surface area
BSC	best supportive care
BUN	blood urea nitrogen
°C	degrees Centigrade
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CLL	chronic lymphocytic leukemia
cm	centimeter
C_{max}	maximum serum concentration
CMH	Cochran Mantel-Haenszel
CML	chronic myeloid leukemia
CNS	central nervous system
CR	complete remission

Abbreviation	Definition
CRA	clinical research associate
CRF	case report form
CRi	complete remission with incomplete hematological recovery
CRM1	chromosome region maintenance 1
CRp	complete remission with incomplete platelet recovery
CRR	complete remission rate
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
DCR	disease control rate (CR, CRi, PR, SD $\geq$ 4 weeks)
DFS	disease-free survival
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
ELN	European LeukemiaNet
EQ-5D-5L	European Quality of Life Five Dimension Five Level Scale
F%	oral bioavailability
°F	degrees Fahrenheit
FACT-Leu	Functional Assessment of Cancer Therapy - Leukemia
FDA	Food and Drug Administration
FR	favorable risk
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor

Abbreviation	Definition
GRAS	generally regarded as safe
GRP	growth regulatory protein
GSH	glutathione
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HPLC/MS-MS	high performance liquid chromatography/tandem mass spectrometry
HR	hazard ratio
hr	hour
IB	Investigator's Brochure
IBD	irritable bowel disease
IC_{50}	inhibitory concentration, 50% (half maximal inhibitory concentration)
ICF	informed consent form
ICH	International Conference on Harmonisation
IFNα	interferon alpha
IFNγ	interferon gamma
IL1α	Interleukin 1 alpha
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-10	Interleukin 10
INR	international normalization ratio
IR	intermediate risk
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IWG	International Working Group
IWRS	interactive web response system
kg	kilogram
KM	Kaplan-Meier
LAFB	left anterior fascicular block
LD	low dose
LDH	lactic dehydrogenase

Abbreviation	Definition
LMW	low molecular weight
LOCS III	Lens Opacities Classification System III
MCP1	monocyte chemoattractant protein-1
mCRR	modified complete remission rate
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MLFS	morphologically leukemia-free state
mg	milligram
MI	myocardial infarction
MIC-1	Macrophage inhibitory chemokine-1
min	minute
mITT	modified intent-to-treat
mL	milliliter
MM	multiple myeloma
mmHg	millimeters of mercury
MMRM	mixed model repeated-measures analysis of variance
MTD	maximum tolerated dose
mRNA	messenger ribonucleic acid
5'NT	5'-nucleotidase
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NK1R	neurokinin 1 receptor
NYHA	New York Heart Association
ORR	overall response rate (CR, CRi)
OS	overall survival
OS3.0	overall survival at least 3 months
PC	Physician's choice
PDn	pharmacodynamics
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic
po	by mouth

Abbreviation	Definition
PP	per protocol
PR	partial remission
PT	prothrombin time
PTCL	peripheral T-cell lymphoma
PTT	partial thromboplastin time
qd	once daily
qhs	at bedtime
QoL	quality of life
qRT-PCR	quantitative real time polymerase chain reaction
RBBB	right bundle branch block
RBC	red blood cell
rIL-11	recombinant Interleukin-11
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAM	S-adenosylmethionine
sc	subcutaneous
SCT	stem cell transplantation
SD	stable disease (within clinical context) standard deviation (within statistical context)
SEER	surveillance, epidemiology, and end result
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SINE	selective inhibitor of nuclear export
SOC	standard of care (within treatment context) system organ class (within adverse event context)
SOP	standard operating procedure
SPC	Summary of Product Characteristics
TK	toxicokinetic
T_{max}	time to maximum serum concentration
TNFα	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
TSP	tumor suppressor protein
TOI	trial outcomes index

Abbreviation	Definition
μL	microliter
ULN	upper limit of normal
VEGFα	vascular endothelial growth factor alpha
WBC	white blood cell
WC	withdrew consent
WHO	World Health Organization
WM	Waldenström's Macroglobulinemia
XPO1	exportin 1

1. OVERVIEW

The nuclear export of most tumor suppressor proteins (TSP) and other growth modulators inactivates their anti-cancer and regulatory functions. The vast majority of TSPs are exported from the nucleus *exclusively* by exportin 1 (XPO1, also called CRM1). Selinexor (KPT-330) is an orally bioavailable, selective inhibitor of nuclear export (SINE) that specifically blocks XPO1, leading to the nuclear accumulation and re-activation of TSP and other growth modulators. The reactivation of multiple tumor suppressor and growth regulatory pathways through inhibition of a non-redundant, single protein represents a novel approach to the treatment of neoplastic diseases including those with multiple genomic alterations and resistance mechanisms.

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, accounting for over 80% of all acute leukemias in individuals aged > 18 years. AML is predominantly a disease of older adults, with a median age at diagnosis of over 65 years. For the growing number of older patients with AML where intensive chemotherapy is associated with unacceptable mortality, therapeutic options are severely limited and median overall survival (OS) is < 1 year. Single agent 'low-dose' cytosine arabinoside (LD-AraC) is the only agent to show a clear reduction in mortality in this population of AML patients. The hypomethylating agent decitabine has shown a trend to improved OS (7.7 months) versus best supportive care ± LD-AraC (5.0 months). The related hypomethylating agent azacitidine has also shown activity in older patients with AML, with improved OS (10.4 months) versus conventional care regimens (6.5 months) (Dombret 2014). Despite some increases in response rates, no other agent has shown a clear improvement in OS in this population, where both efficacy and low rates of side effects are critical.

Selinexor (oral) has shown single-agent, durable, anti-cancer activity in patients with multiply relapsed or refractory hematologic and solid tumor malignancies in initial Phase 1 dose escalation studies. Elderly patients (median age 68 years) with heavily pretreated AML whose life expectancy is very short were included in the initial phase 1 studies, and durable complete remissions (CR), complete remissions with incomplete hematologic recovery (CRi/p), partial remissions (PR) and stable disease (SD) were observed in these patients. With standard supportive care for selinexor-induced anorexia and fatigue, long-term tolerability has been adequate with no acute toxicities or major organ damage, even in patients > 70 years of age. Therefore, oral selinexor may represent a novel treatment for AML in this difficult-to-treat population.

This randomized, open label study has been designed to assess whether oral, single agent selinexor can improve the OS in patients with relapsed or refractory AML who are not candidates for intensive chemotherapy.

2. NUCLEAR EXPORT

Neoplasms must inactivate most or all of the > 10 major tumor suppressor pathways in order to perpetuate their phenotypes (Sharpless 2007). Since the vast majority of tumor suppressor (TSP) and other growth modulators require nuclear localization in order to carry out their antineoplastic activities, enhancing their nuclear export leads to their functional inactivation. The control of nuclear import and export is tightly regulated by shuttle proteins in eukaryotic cells. There are over 15 nuclear import proteins, or importins, but only seven (7) nuclear export proteins, or exportins (Exportins 1-7). Despite their marked diversity of sequence, size, and 3-dimensional structures, the major TSP/growth regulatory proteins (GRP) are exported exclusively by the protein Exportin 1 (XPO1), also called chromosome region maintenance 1 (CRM1). All malignancies studied to date, including acute myeloid leukemia (AML), show elevated XPO1 levels, and increasing levels often correlate with poorer prognosis (Huang 2009, Yao 2009, van der Watt 2009, Liu 2009, Kojima 2013, Tai 2014, Lapalombella 2012). Elevated XPO1 levels lead to cytoplasmic mislocalization and functional inactivation of TSP/GRP. It appears that tumor cells have co-opted XPO1 to move TSP/GRP out of the nucleus, thereby neutralizing their anti-neoplastic functions.

XPO1 inhibitors have been shown to block the nuclear export of key TSP, leading to accumulation of these proteins in the nucleus, as nuclear import appears to proceed unimpeded. Moreover, nuclear retention appears to prevent proteasome-mediated degradation (which is typically cytoplasmic). Forced nuclear retention of TSP can counteract a multitude of oncogenic (and inflammatory) pathways that perpetuate the neoplastic phenotype (Table 2). Moreover, certain proteins such as survivin (Stauber 2007) and p21CIP1 (Gartel 2002) can be anti-apoptotic when in the cytoplasm; forcing their nuclear retention by XPO1 inhibition can prevent their anti-apoptotic functions and, for p21, expose its antitumor activities.

Table 2: Effect of XPO1 Inhibition on Oncogenic and Inflammatory Pathways

Pathway Affected	Effect of XPO1 Inhibition	Reference
p53 mutation	p73 activation, p21 activation	Ranganathan 2012
MDM2 activation	Nuclear p53 retention and activation	Kojima 2013
NPM1 mutation	Restoration of nuclear NPM1	Falini 2007
CEBPA down-regulation	Nuclear retention and activation	Ranganathan 2012
XPO1 overexpression	XPO1 reduction	Walker 2013
FLT3 activation	FLT3 reduction	Ranganathan 2012
KIT activation	KIT reduction	Ranganathan 2012
NF-κB activation	IκB nuclear retention and activation	Lapalombella 2012
PIK3 or AKT activation	FOXO1, -3, -4 activation	Lapalombella 2012
Survivin – cytoplasmic	Survivin nuclear retention	Altura 2003
Bcr-Abl activation	PP2A activation	Walker 2013

3. ACUTE MYELOID LEUKEMIA (AML)

AML is the most common form of acute leukemia in adults, accounting for over 80% of all acute leukemias in individuals aged > 18 years (Thein 2013). An estimated 20,830 people will be diagnosed with AML in the United States in 2015 and 10,460 patients will die of the disease (American Cancer Society 2015). Although survival rates have almost doubled for AML in the youngest age group, there has been little improvement in survival for adults in the older age groups, with overall 5-year survival rates still less than 5% (Xie 2003). A subsequent analysis based on the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) dataset including 19,000 AML patients provided similar results; although overall survival improved consistently over the past three decades in patients ages 65 to 74 years, with improvements in 12-month survival from 20% (1977-1986), to 25% (1987-1996), to 30% (1997-2006), respectively, survival rates did not improve in patients aged ≥ 75 years. In this study, the highest age group (≥ 85 years) had the lowest survival rates, with no apparent improvement compared to previous years (Thein 2013).

Consistent with the aging of the US population, the median age of AML patients at diagnosis has increased from 68 to 72 years (Motyckova 2011). AML is a heterogeneous disease with a wide variety of genetic abnormalities, rapid and diverse clonal evolution, and rapid generation of resistance to standard agents. Comorbid conditions and general health make therapeutics options in older patients very limited. Because standard chemotherapy (typically an anthracycline plus standard dose AraC) for AML is quite toxic, only 30-35% of older adults are even considered for this treatment (Isidori 2013). For those older adults with AML who do receive standard chemotherapy, compared with younger patients, there is a higher incidence of therapy-associated early death (~20% versus < 10%), a lower rate of complete remission (45-65% versus ~80%), and a reduced chance of long-term survival (Yanada 2012). Despite the achievement of CR in approximately half of the older patients receiving standard induction chemotherapy, the overall survival from diagnosis remains < 1 year. Moreover, the increased morbidity and mortality during induction appear to be directly related to age.

For older patients who are deemed unfit to receive standard intensive induction chemotherapy due to expected therapy-related mortality >30%, survival is very poor. Single agent LD-AraC is the only agent to show a clear reduction in mortality in this population of AML patients (Burnett 2007). The hypomethylating agent decitabine has shown a trend to improved OS (7.7 months) versus best supportive care ± LD-AraC (5.0 months). The related hypomethylating agent azacitidine has shown activity in older patients with AML, with improved OS (10.4 months) versus conventional care regimens (6.5 months) (Dombret 2014). Despite some increases in response rates, no other agent has shown a clear improvement in OS in this population, where both efficacy and low rates of side effects are critical (see e.g., Burnett 2013). The treatment of older patients with AML following initial relapse from or progression on front-line therapy is even more challenging.

An oral agent that can be administered in the outpatient setting, shows anti-leukemic activity with acceptable tolerability, low incidence of induction-associated death and other acute toxicities would be welcomed in the treatment of elderly patients with relapsed/refractory AML.

4. SELINEXOR (KPT-330)

4.1. Introduction

Selinexor is an oral, first in class, irreversible, potent and Selective Inhibitor of Nuclear Export (SINE) compound that specifically blocks Exportin 1 (XPO1/CRM1). Selinexor restores many of the tumor suppressor (TSP) and growth regulatory (GRP) proteins to the nucleus where they can carry out their normal functions. It is selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both *in vitro* and *in vivo*. All cell types exposed to SINE compounds *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 intrinsically cytotoxic; rather, they can restore the highly effective tumor suppressing pathways that lead to selective elimination of genomically damaged (i.e., neoplastic) cells. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared.

4.2. Preclinical Data

In this section a short summary of preclinical data is provided. More detailed information is presented in the *Selinexor/KPT-330 Investigator's Brochure (IB)*.

4.2.1. Pharmacology Studies

AML cells overexpress the nuclear exporter, Exportin 1 (XPO1/CRM1) and higher XPO1 levels correlate with poor outcome (Kojima 2013). The novel SINE compound 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 (Ranganathan 2012).

Mechanistic studies show that SINE compounds induces nuclear localization and activation of multiple tumor suppressor proteins (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 compounds treatment in both *FLT3*-ITD and wild-type cell lines (Ranganathan 2012). Selinexor treatment also restored the localization of cytoplasmic mutant NPM1 into the nucleus.

In murine AML and ALL models, selinexor showed potent antileukemic activity without toxicity to normal hematopoietic cells (Etchin 2013a, Etchin 2013b; Ranganathan 2012).

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.

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 KPT-330 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 KPT-330. 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 KPT-330 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 KPT-330 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/KPT-330 IB* for more information.

4.3. 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 RP2D in patients with hematological malignancies with three arms. Arm 1 includes patients with "chronic" hematological malignancies multiple myeloma (MM), Waldenström's Macroglobulinemia (WM), non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL). This trial enrolled 2 patients 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, the standard 3+3 design was used with dose escalation increase of 30-40% from previous cohort. Arm 2 includes patients with acute myeloid leukemia (AML) of any subtype except M3. Because of the rapidly progressive nature of AML, Arm 2 began dosing at 16.8 mg/m^2 after dose limiting toxicity (DLT) clearance in cohort 3 (12 mg/m^2) and initiation of 16.8 mg/m^2, corresponding to Cohort 4 of the Chronic Hematological Malignancies portion of the study. The standard 3+3 design was used with 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.

A dose of 70 mg/m^2 (~120 mg fixed dose) cleared DLT in patients with relapsed/refractory AML in Study KCP-330-001. An ~55 mg/m^2 twice weekly dose was initially used in this study (Protocol Versions< 5.0) as this was <MTD. However, the dose has been reduced to a 60 mg fixed dose in response to a possible increase in sepsis related SAEs for selinexor ~55 mg/m^2

(8 sepsis events) versus PC (2 sepsis events) (a ratio of 4:1 and not the expected 2:1) that was detected during an annual review of clinical safety data (29 July 2015). Clinical safety data supporting the 60 mg fixed dose are provided in Section 4.3.1.1.

Overview of Clinical Efficacy in AML. Sixty-five heavily pretreated patients with progressive RR AML, most with ≥ 3 prior lines of treatment, were enrolled in the KCP-330-001 AML treatment arm and received selinexor 16.8-70 mg/m^2 in four-week cycles.

Among 48 evaluable patients (of 65 patients enrolled), the CR rate, with or without full hematologic recovery, was 8%, ORR was 15%, and DCR was 49%. (Note: 17 patients [26%] were non-evaluable but were included in the AML response rate calculation, based on the ITT approach.) Best response results as of 10 June 2014 are shown in Table 3 (Garzon 2014). Patients could be deemed non-evaluable due to either lack of post-dosing bone marrow assessments, failure to take the required number of doses of study medication, withdrawal of consent, or death during Cycle 1 prior to response determination. During this study, sixteen patients died during Cycle 1, including patients who were evaluable due to PD prior to death.

Table 3: Best Responses in AML Patients as of 10 June 2014

Number Enrolled	DCR (%)	ORR (%)	CR (%)	CR(i/p) (%)	PR (%)	MLFS (%)	SD (%)	PD (%)	NE (%)
65	31	10	5	2	1	2	22	16	17
(100%)	(49%)	(15%)	(8%)	(3%)	(2%)	(3%)	(34%)	(25%)	(26%)

Abbreviations: N=number of patients, CR=complete remission, CR(i/p)=complete remission without hematological recovery, PR/MLFS= partial remission / morphologic leukemia free state, SD=stable disease, PD=progressive disease, NE=non-evaluable.

Overview of Clinical Safety in AML. As of the 31 May 2015 clinical safety analysis for selinexor studies in patients with hematological malignancies, Grade 3/4 TEAEs that were reported in ≥ 5% of patients include: anemia (13%) and fatigue (11%). Grade 3/4 thrombocytopenia (27%) and neutropenia (15%) were observed, however all patients enrolled in selinexor clinical studies had advanced stages of cancer and have been heavily pre-treated with chemotherapy and other marrow-suppressive agents, which may contribute to reported instances of myelosuppression. The most common Grade 1/2 TEAEs were nausea (50%), fatigue (40%), anorexia (36%), and vomiting (28%).

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.

Please refer to the *Selinexor/KPT-330 IB* for the most current clinical experience information.

4.3.1. 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) V4.03. 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 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.

As of the 31 May 2015 clinical safety analysis for all selinexor studies, the most common AEs suspected to be related to selinexor (incidences in parentheses) have been nausea (55%), fatigue (54%), anorexia (43%), vomiting (35%), and thrombocytopenia (30%). Most of these effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing.

Low-grade blurred vision was reported in 12% of patients treated with selinexor. In patients without pre-existing cataracts, blurred vision was not associated with objective findings of lens opacity (or other abnormalities) on expert ophthalmic examination. The cases have generally been self-limiting without progression, even when selinexor dosing was continued.

In a previous study, one patient, heavily pre-treated for recurrent pancreatic cancer, developed acute cerebellar syndrome following 3 doses of selinexor at 85 mg/m^2 BSA twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. Since the date of the initial reported event, this patient is recovering, with both speech and mobility recovered to near baseline over ~6 weeks. No other patients have reported similar symptoms to date.

Cognitive disturbance (Grade 3) was experienced by an 18-year-old female patient with relapsed AML after receiving four doses of selinexor 56 mg/m^2 twice weekly in the dose-escalation phase of a pediatric investigator sponsored trial.

Please refer to the *Selinexor/KPT-330 IB* for the most current safety information.

4.3.1.1. Risk of Sepsis in AML

During an annual review of clinical safety data (29 July 2015), a possible increase in sepsis-related SAEs for selinexor ~55 mg/m^2 (8 sepsis events) versus PC (2 sepsis events) in AML was detected in the patient population for this study.

The incidence of febrile neutropenia was similar on the two arms of the study (17 vs 9 events on selinexor and PC arms, respectively), although pneumonia/lung infections may be increased on the selinexor arm (8 vs 2 events on selinexor and PC arms, respectively). Seven of the 8 sepsis events on the selinexor arm occurred in patients receiving 100 mg of selinexor; the other patient received 80 mg of selinexor. Although the numbers are small, these observations suggest that doses above 80 mg of selinexor should not be given to older patients with relapsed/refractory AML.

In parallel with these observations and with the preparation of the Phase 1 study updates for the selinexor annual report, AE rates were compiled across dose levels for patients with AML in the initial Phase 1 study (Study KCP-330-001). Rates of sepsis, but not other infections, appear to be higher at doses > 300 mg/m^2/cycle than at doses ≤ 300 mg/m^2/cycle. Similar findings were not observed for other indications in other studies across other hematologic and solid tumor malignancies.

Based on these safety analyses, the dose of selinexor in this study has been reduced from an oral fixed milligram (mg) dose equivalent to ~55 mg/m^2 (60, 80, 100 or 120 mg based on body surface area (BSA); ~ 440 mg/m^2/cycle) dosed twice weekly during each 4-week cycle to a fixed dose of 60 mg (~35 mg/m^2, ~280 mg/m^2/cycle) dosed twice weekly during each 4-week cycle.

4.3.1.2. Reproductive Risks

Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies; most resolved or partially resolved during the recovery period. The long term effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development. Please see the *Selinexor/KPT-330 IB* for additional information. As it is unknown if selinexor produces any reproductive toxicity in humans, all patients must agree to use effective contraception (see Section 12.3.3.1 *Prevention of pregnancy*) during the study and for 3 months after the end of treatment.

5. RATIONALE FOR THE STUDY

Selinexor is a first in class SINE compound that specifically blocks the karyopherin protein Exportin 1 (XPO1/Exportin 1, also called CRM1). XPO1 is a non-redundant, key regulatory protein responsible for the nuclear export and therefore functional inactivation of tumor suppressor proteins (TSPs). XPO1 is up-regulated in AML and correlated with poor prognosis (Kojima 2013). Selinexor, given orally, has demonstrated potent anti-leukemic activity in animal models of AML with minimal toxicity to normal hematopoietic cells (Ranganathan 2012; Etchin 2013a; Etchin 2013b).

As of 10 June 2014, 65 patients with relapsed/refractory AML (median prior therapies 3) were enrolled in the ongoing Phase 1 study (KCP-330-001) at doses of 16.8 mg/m^2 to 70 mg/m^2. The median age was 67 years. The most common toxicities have been diarrhea, nausea, anorexia and fatigue. Nausea, anorexia and fatigue were manageable with oral supportive care agents. Diarrhea generally responded rapidly to standard anti-diarrheal agents. As of 10 June 2014, there has been no DLT. Along these lines, selinexor-associated deaths have not been reported. Of the 48 patients (out of 65 patients enrolled) who were evaluable for response, complete remission (CR) with full hematological recovery was achieved in 5 patients (8%), and CR without hematological recovery (CRi) in 2 patients (3%). Partial remission (PR) was achieved in 1 patient (2%). A morphological leukemia free state was achieved in 2 patients (3%). Twenty-two (34%) patients have had stable disease (SD) and 16 (25%) have had progressive disease (PD) (Garzon 2014).

The goal of this trial is to evaluate the potential for an overall survival (OS) benefit associated with oral selinexor administration in patients ≥ 60 years of age that are ineligible for intensive chemotherapy or stem cell transplantation (SCT).

5.1. Rationale for the Doses and the Dosing Regimen

A MTD of 65 mg/m^2 (~110 mg) twice weekly (Days 1 and 3) has been determined in the ongoing Phase 1 study of selinexor in patients with advanced solid tumors (KCP-330-002). Two dose-limiting toxicities (DLTs) occurred in 2 patients in the solid tumor study (KCP-330-002) treated at 85 mg/m^2 (~145 mg) twice weekly and included 'probably related' asymptomatic Grade 3 hyponatremia and 'possibly related' acute cerebellar syndrome with ataxia and dysarthria. Of note, asymptomatic hyponatremia had been observed in other patients treated with selinexor, but only this one case of acute cerebellar syndrome was observed across any of the selinexor trials (730 patients evaluable for safety as of 31 May 2015).

A dose of 70 mg/m^2 (~120 mg fixed dose) cleared DLT in patients with relapsed/refractory AML. Therefore the ~55 mg/m^{2}twice weekly dose used in Protocol Versions< 5.0 was <MTD. However, the dose has been reduced in response to a possible increase in sepsis related SAEs for selinexor ~55 mg/m^2 (8 sepsis events) versus PC (2 sepsis events) (a ratio of 4:1 and not the expected 2:1) that was detected during an annual review of clinical safety data (29 July 2015). Clinical safety data supporting the 60 mg fixed dose are provided in Section 4.3.1.1.

Selinexor will be initiated at a fixed oral dose of 60 mg (equivalent to ~35 mg/m^2 mg/m^2) twice weekly (e.g., Monday and Wednesday or Tuesday and Thursday or Wednesday and Friday).

Patients who were randomized to selinexor (~55 mg/m^2) under Protocol Versions < 5.0 will be switched to the 60 mg fixed dose.

No patients in any study may receive doses above 70 mg/m^2. Therefore, BSA will be monitored to ensure that no patient exceeds the maximum allowable dose.

6. STUDY OBJECTIVES

6.1. Primary Objective

To determine overall survival (OS) of selinexor as compared to physician's choice (PC) in patients ≥ 60 years old with relapsed/refractory AML that requires treatment and are ineligible for intensive chemotherapy and/or transplantation.

6.2. Secondary Objectives

- To determine the proportion of patients whose OS is at least 3 months (OS3.0)
- To determine the complete remission rate (CRR), including complete remission with full hematologic recovery (CR), and median disease free survival (DFS) for patients who achieve CR
- To determine the modified CRR (mCRR), including CR or complete remission with incomplete hematologic recovery (CRi) (including complete remission with incomplete platelet recovery [CRp]), and median DFS for patients who achieve CR or CRi (including CRp)
- To determine the overall response rate (ORR) and duration of overall response (DOR), including CR, CRi, morphologic leukemia-free state (MLFS), and partial remission (PR)
- To determine the disease control rate (DCR) defined as ORR + stable disease for ≥ 4 weeks (SD), and duration of DCR
- To assess the safety and tolerability of selinexor (KPT-330), as compared to physician's choice (PC)
- Quality of life and patient reported outcomes (FACT-Leukemia and EQ-5D-5L) (QoL)

7. STUDY DESIGN

7.1. Study Design Overview

This is a randomized, multicenter, open-label Phase 2 study of the SINE compound selinexor given orally versus restricted investigator choice (i.e., one of three potential salvage therapies).

Patients who have never been transplant-eligible, are currently deemed unfit for intensive chemotherapy, ≥ 60 years old, who have AML (except acute promyelocytic leukemia: APL, AML M3) who have poor prognosis (intermediate or adverse risk) cytogenetics, with relapsed or refractory AML, after at least one prior AML therapy including at least an adequate trial of a hypomethylating agent with at least 2 cycles, and are meeting the inclusion and exclusion criteria will be randomized to receive either oral selinexor or physician's choice (one of three potential treatments: best supportive care (BSC) alone, or BSC + hypomethylating agent, or BSC + low dose AraC) until disease progression, death or intolerance has occurred.

Patients will be stratified for randomization using three criteria: (1) duration of their first CR on prior therapy, > 6 months versus ≤ 6 months or never achieved CR; (2) number of prior therapies, 1 versus >1; (3) peripheral leukemic blast counts ≥ 10,000/μL versus < 10,000/μL.

Patients can be randomized within 3 calendar days of Cycle 1 Day 1. Any patient randomized into this trial cannot be re-randomized for any reason. Selinexor will be given orally twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, or Wednesday and Friday) at a dose of 60 mg. Patients who were randomized to selinexor (~55 mg/m^2) under Protocol Versions < 5.0 will be switched to the 60 mg fixed dose. Clinical safety data supporting the 60 mg fixed dose are provided in Section 4.3.1.1.

Hydroxyurea may be used at any time during the study, typically in patients with WBC ≥ 30,000/μL or per institutional guidelines. Prior to the initiation of hydroxyurea, please consider the contraindications in the Summary of Product Characteristics (SPC), including leukocytopenia (< 2.5 x 10^9 leukocytes/L), thrombocytopenia (< 100 x 10^9 platelets/L) or severe anemia.

One of the following three conventional care regimens will be selected by the treating physician: (1) best supportive care (BSC) including blood product transfusions, antimicrobials, growth factors as needed, and hydroxyurea; or (2) BSC + low dose AraC, 20 mg bid by subcutaneous (sc) injection daily on days 1-10/14 days (20/28 doses) to be repeated at 28 to 42 day intervals; or (3) BSC + hypomethylating agent: azacitidine 75 mg/m^2 by sc injection daily on Days 1-7 or Days 1-5, 8-9 (7 doses) to be repeated at ≥ 28 day intervals, *or* decitabine (20 mg/m^2 IV over 1 hour daily on days 1-5 or days 1-10 to be repeated at ≥ 28 day intervals).

Patients on the selinexor arm can receive appropriate anti-leukemia therapy following progression on or withdrawal from the selinexor arm.

Treatment with selinexor or the physician's choice will continue until the patient is removed from the study. At the discretion of the investigator, the investigator may remove a patient from study treatment for the following reasons:

- Disease progression defined as an increase in blast counts and absence of hematologic recovery (one or more lineages)
- Unacceptable AEs or failure to tolerate the study treatment
- Patients decides to discontinue study therapy
- Significant deviation from entry criteria (e.g., non-relapsed or non-refractory AML)
- Misuse of study medication (e.g., deliberate overdosing by patient)
- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk
- Any other medically appropriate reason or significant protocol violation, in the opinion of the investigator.

The investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the eCRF. Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment at a later date.

Patients may decide to discontinue study treatment for any reason. Patients who elect not to initiate study treatment or to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial.

Patients will be followed for survival until the last patient has been followed for 6 months from the end of treatment, disease progression, another withdrawal criterion is met, or until death, whichever comes first.

7.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be set up to review the safety of selinexor and to review any SAEs that occur during the study.

The DSMB will be composed of at least two physicians (at least one of whom is an oncologist) and a statistician. The DSMB will be provided with all reports of SAEs regardless of investigator causality assessments.

Two interim analyses will be conducted on the ITT population (see Section 14.2.1.4 for further details). The first interim analysis will take place after 31 (25%) OS events have occurred, and will be conducted to assess futility only (non-binding). Futility would be concluded if the p-value from the log-rank test is ≥ 0.8084. The second interim analysis will take place after 62 (50%) deaths, and will allow for a conclusion of significant efficacy at an α-level < 0.0015, and stopping for futility (non-binding) at an α-level ≥ 0.2879. The DSMB will be given the results of the interim analyses for review and will provide to Karyopharm the recommendation of stopping the trial for significant efficacy or futility, or continuing the study.

In addition to the interim analyses performed on the ITT population, a review of safety data for all patients will also be conducted at each interim analysis.

Following the initial meeting, DSMB meetings will occur on a periodic basis in accordance with the DSMB charter. The chairperson of the DSMB will also be immediately provided with the report of any SAE that is judged as possibly, probably, or definitely attributable to treatment with study drug.

The charter of the DSMB will specify that this committee is charged with providing periodic reports to Karyopharm that contain recommendations that include, but are not limited to, (a) continuation of the study, and (b) termination of the study.

7.3. Stopping Rules

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in Section 11: Discontinuation Criteria.

7.4. Study Endpoints

7.4.1. Primary Endpoint(s)

Overall survival (OS) is the primary efficacy endpoint of this study.

7.4.2. Secondary Endpoints

Secondary efficacy endpoints will include the following, assessed in hierarchical fashion in the order presented below:

- The proportion of patients whose OS is at least 3 months (OS3.0)
- The complete remission rate (CRR), including complete remission with full hematologic recovery (CR), and median disease free survival (DFS) for patients who achieve CR
- The modified CRR (mCRR), including CR or CRi (including CRp), and median DFS for patients who achieve CR or CRi (including CRp)
- The overall response rate (ORR) and duration of overall response (DOR), including CR, CRi, MLFS, and partial remission (PR)
- The disease control rate (DCR) defined as ORR + stable disease for ≥ 4 weeks (SD), and duration of DCR
- Quality of life and patient reported outcomes (FACT-Leukemia and EQ-5D-5L) (QoL)

The safety and tolerability of selinexor and PC will be evaluated by means of drug-related AE reports, physical examinations, and laboratory safety evaluations.

7.5. Blinding and Randomization

This is an open-label study and is, therefore, not blinded.

Patients will be randomized into the selinexor or PC treatment arms in a 2:1 allocation, within each of the 2 x 2 x 2 stratification levels. Patients will be stratified for randomization using

three criteria: (1) duration of their first CR on prior therapy, > 6 months versus ≤ 6 months or never achieved CR; (2) number of prior therapies, 1 versus >1 (3) peripheral leukemic blast counts ≥ 10,000/μL versus < 10,000/μL. Patients should be randomized within 3 calendar days of Cycle 1 Day 1.

Any patient randomized into this trial cannot be re-randomized for any reason.

8. SELECTION OF PATIENTS

8.1. Number of Patients

Approximately 300 patients will be randomized into the selinexor or PC treatment arms in a 2:1 allocation, with the 2:1 allocation performed within each of the 2 x 2 x 2 stratification levels. Two separate cohorts will be randomized. To date, approximately 110 patients were randomized to selinexor at a fixed dose of ~55 mg/m^2 versus PC under Protocol Versions < 5.0; enrollment will continue until Protocol Version 5.0 is approved. Due to dose and inclusion criteria changes in Version 5.0, the patients enrolled under Protocol Versions < 5.0 will not be included in the ITT population. Approximately 171 additional patients will be randomized under Protocol Versions ≥ 5.0, to either 60 mg of selinexor (flat dose) or PC, again in a 2:1 randomization allocation within strata.

8.2. Recruitment

This study will be conducted at approximately 60 sites in North America, Europe, and the rest of the world.

8.3. Inclusion Criteria

In order for a patient to be included in the study, the patient must meet all the following criteria:

1. Signed, written informed consent in accordance with federal, local, and institutional guidelines
2. Patients age ≥ 60 years with relapsed/refractory AML (defined using WHO criteria) of any type except for acute promyelocytic leukemia (APL; AML M3), after at least one prior AML therapy, who have never undergone and who are not currently eligible for stem cell transplantation, and are currently deemed unfit for intensive chemotherapy.
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
4. Diagnosis of AML (WHO classification definition of ≥ 20% blasts) with the exception of acute promyelocytic leukemia (APL; AML M3); patients must have available archival or recently acquired bone marrow biopsy/aspiration or tumor tissue for central review to be eligible.
5. Relapsed or refractory AML, defined as either:
   1) recurrence of disease after a complete remission (CR), or
   2) failure to achieve CR with initial therapy.
6. All patients must have received at least one prior line of AML therapy given at standard doses and must have progressed after their most recent therapy. Prior therapy must have included an adequate trial of a hypomethylating agent with at least 2 cycles.
7. A period of at least 2 weeks must have elapsed since the last anti-leukemia treatment (with the exception of hydroxyurea) before first dose in this study.
8. Objective, documented evidence of disease progression or failure to respond to a reasonable trial of their most recent previous therapy prior to study entry.
9. Serum biochemical values with the following limits unless due to leukemia: creatinine clearance > 30 cc/min calculated using the Cockcroft and Gault (Cockcroft and Gault 1976) formula or measured; total bilirubin ≤ 2 x upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must

have a total bilirubin of ≤ 3 x ULN); transaminases (AST and ALT) ≤ 2.5 x ULN (except patients with known liver involvement of their AML who must have an AST and ALT ≤ 5 x ULN).

10. Coagulation time (Prothrombin time [PT] and partial thromboplastin time [PTT]) ≤ 1.5 x ULN (PTT elevation for known lupus anticoagulant is allowed). Coagulation may also be measured using thromboplastin time (Quick test) if measurement of PT/PTT is not feasible.
11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.
12. Male patients with partners of childbearing potential must agree to use effective contraception during the study period and a period of 3 months after the last dose of study drug.

8.4. Exclusion Criteria

A patient will not be included in the study if any of the following criteria are met:

1. Treatment with any investigational agent within three weeks prior to first dose in this study.
2. Presence of central nervous system (CNS) leukemia.
3. Patients with AML M3 or who are in blast transformation of chronic myeloid leukemia (CML). Prior myelodysplastic syndrome (MDS) is acceptable; prior treatment for MDS does not count as an AML therapy.
4. Patients whose AML is classified as favorable according to the European LeukemiaNet (ELN) disease risk assessment (Appendix 1).
5. Major surgery within 2 weeks of first dose of study drug. Patients must have recovered from the effects of any surgery performed greater than 2 weeks previously.
6. Patient has a concurrent active malignancy.
7. Unstable cardiovascular function:
   - symptomatic ischemia, or
   - uncontrolled clinically significant conduction abnormalities (i.e., ventricular tachycardia on antiarrhythmic agents are excluded; 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
   - congestive heart failure (CHF) NYHA Class ≥ 3, or
   - myocardial infarction (MI) within 3 months.
8. Uncontrolled infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose. Infections controlled on concurrent anti-microbial agents are acceptable, and anti-microbial prophylaxis per institutional guidelines are acceptable.
9. 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).
10. Known human immunodeficiency virus (HIV) infection.
11. Any medical condition which, in the investigator's opinion, could compromise the patient's safety.

12. Patients unable to swallow tablets, or patients with malabsorption syndrome, or any other disease significantly affecting gastrointestinal function.

8.5. Screen Failures

Patients who sign an informed consent form, are not assigned to a treatment, and do not receive test article are defined as screen failures. For all screen failures, the investigator will enter the screening number, patient initials and reason(s) for screen failure into the electronic data capture (eDC) system. These data will also be retained in the investigator's study files and can be printed by the site in log format at the end of the study. Screen failures are to be replaced.

9. STUDY PLAN AND PROCEDURES

This is a randomized, multicenter, open-label Phase 2 study of the SINE compound selinexor given orally versus investigator choice (one of three potential salvage therapies).

Patients age ≥ 60 years with relapsed/refractory AML (defined using WHO criteria) of any type except for APL (AML M3), who have poor prognosis (intermediate or adverse risk) cytogenetics, with relapsed or refractory AML, after at least one prior AML therapy (must have included an adequate trial of a hypomethylating agent with at least 2 cycles), who have never undergone, and who are not currently eligible for, stem cell transplantation, and are currently deemed unfit for intensive chemotherapy, and are meeting the inclusion and exclusion criteria will be randomized to receive either oral selinexor or investigator choice (one of three potential treatments: best supportive care (BSC) alone, or BSC + hypomethylating agent, or BSC + low-dose AraC until disease progression, death, or intolerance has occurred.

Patients on the selinexor arm can receive appropriate anti-leukemia therapy following progression on or withdrawal from the selinexor arm.

9.1. Study Patient Number

Approximately 300 patients will be randomized into the selinexor or PC treatment arms in a 2:1 allocation, with the 2:1 allocation performed within each of the 2 x 2 x 2 stratification levels. Two separate cohorts will be randomized. To date, approximately 110 patients were randomized to selinexor at a fixed dose of ~55 mg/m^2 versus PC under Protocol Versions < 5.0; enrollment will continue until Protocol Version 5.0 is approved. Due to dose and inclusion criteria changes in Version 5.0, the patients enrolled under Protocol Versions < 5.0 will not be included in the ITT population. Approximately 171 additional patients will be randomized under Protocol Versions ≥ 5.0, to either 60 mg of selinexor (flat dose) or PC, again in a 2:1 randomization allocation within strata. Patients will be stratified for randomization using three criteria: (1) duration of their first CR on prior therapy, > 6 months versus ≤ 6 months or never achieved CR; (2) number of prior therapies, 1 versus >1; (3) peripheral leukemic blast counts ≥ 10,000/μL versus < 10,000/μL.

Each patient is identified in the study by a patient number that is assigned when the patient is first screened and is retained as the primary identifier for the patient for the duration of the study. Patient numbers will not be reassigned or reused for any reason. The patient number consists of the last 3 digits of the protocol number, center number as assigned by Karyopharm or the eDC vendor, with a sequential patient number suffixed to it, so each patient is numbered uniquely across the entire database. The investigator must maintain a patient master log.

9.2. Description of Study Days

9.2.1. Visit 1 (within 14 days prior to start of therapy); Screening #1

Study procedures will be performed within 14 days prior to the start of therapy, as specified in Table 1. The study site should not repeat procedures completed as standard of care (SOC) if they are within the Screening window, and prior to signing the Informed Consent Form (ICF).

The data from these procedures are part of the medical history and can be used for study purposes.

- Sign Informed Consent
- Demographics
- Complete medical history
- Full ophthalmic examination (See Appendix 3 for a detailed description).
- Bone Marrow Aspirate (or Biopsy if aspirate is not adequate) including immunophenotyping, cytogenetic and molecular analysis (FLT3 ITD or TKD mutation or NPM1 mutations)(***requires approval of the sponsor to perform between 14 and 8 days prior to Day 1 Cycle 1 Days; typical is ≤7 days prior to Day 1 Cycle 1***)
- 12-lead electrocardiogram (ECG)
- Baseline symptoms
- Concomitant medication assessments
- Chest radiograph
- Disease risk assessment, based on patient disease history, according to the European LeukemiaNet (ELN): Favorable Risk (FR), Intermediate Risk (IR), and Adverse Risk (AR) (Rollig 2011) (See Appendix 1)

9.2.2. Visit 2 (within 7 days prior to start of therapy); Screening #2

Study procedures will be performed within 7 days prior to the start of therapy, as specified in Table 1:

- Review of inclusion and exclusion criteria
- Complete physical examination
- ECOG Performance Status
- Body Surface Area (BSA) calculated by Dubois (Dubois and Dubois, 1916) or Mosteller (Mosteller 1987) method
- Weight, height
- Vital signs (blood pressure, heart rate, body temperature
- Oxygen saturation [Pulse Oximetry])
- Urine dipstick
- Complete serum chemistry
- Coagulation parameters
- Hematology (CBC with differential)
- Bone Marrow Aspirate (or Biopsy if aspirate is not adequate) including immunophenotyping, cytogenetic and molecular analysis (FLT3 ITD or TKD mutation or NPM1 mutations)(if not done during Visit 1)
- Blood draw for correlative studies using peripheral blasts
- Baseline symptoms
- Concomitant medication assessments
- Disease risk assessment according to the European LeukemiaNet (ELN): Favorable Risk (FR), Intermediate Risk (IR) and Adverse Risk (AR) (Rollig 2011) (See Appendix 1) (if not done at Visit 1)

9.2.3. Visits 3, 5, 6, and 7 (Day 1 of each Week, Cycle 1); Return to the Clinic

Patients should be randomized within 3 calendar days of Cycle 1 Day 1 (Visit 3) and those randomized to selinexor treatment should meet with a person who is experienced in giving advice on how food and nutrition affect health on or before C1D1.

Study procedures will be performed on Day 1 (± 1 day) of each week of the 4-week cycle, as specified in Table 1:

- Symptom-directed physical examination
- ECOG Performance Status
- Body Surface Area (BSA)
- Weight
- Vital signs (blood pressure, heart rate, body temperature
- Oxygen saturation [Pulse Oximetry])
- 12-lead electrocardiogram (ECG) (Day 1 of Week 1 of the cycle only)
- Urine dipstick
- Complete serum chemistry
- Coagulation parameters
- Hematology (CBC with differential)
- Selinexor dosing or physician's choice treatment
- Blood draws for pharmacokinetic testing (selinexor group only) on Day 1 of each week
- CCI
- AEs
- Concomitant medication assessments
- Quality of Life (FACT-Leu and EQ-5D-5L) questionnaires will be filled out (Day 1 of Week 1 of the cycle only)
- Review of temperature diary (Visits 5, 6, and 7 only)

9.2.4. Cycles 1-3 Day 4 Only (+ 1 day); C1D1 Visit 4/Phone Calls with Patient

A visit (Visit 4) is required on Cycle 1 Day 4 to monitor adverse events (including infections), to review temperature diaries, to evaluate supportive care medications, and to adjust supportive care as appropriate. Weekly phone calls to the patient may be done in place of visits at Day 4 (+1 day) for all other weeks during Cycles 1-3. The phone contact with the patient must take place on Day 4 (+ 1 day) of weeks 2-4 in Cycle 1 and each week in Cycles 2-3. For patients in the selinexor arm, the weekly phone call follows selinexor dosing on Day 1 of each week.

9.2.5. Visits 8, 10, and 12-17 (Day 1 and 15 of each Cycle - Cycles 2 - 5); Return to the Clinic

Study procedures will be performed on Day 1 and Day 15 (± 2 days) of each cycle, as specified in Table 1:

- Symptom-directed physical examination
- ECOG Performance Status
- Body Surface Area (BSA)

- Weight
- Vital signs (blood pressure, heart rate, body temperature)
- Oxygen saturation [Pulse Oximetry])
- 12-lead electrocardiogram (ECG) (Day 1 of Week 1 of the cycle only)
- Urine dipstick
- Limited serum chemistry
- Coagulation parameters
- Hematology (CBC with differential)
- Bone Marrow Aspirate (or Biopsy if aspirate is not adequate) for disease status assessment as specified in Section 10.13
- Selinexor dosing or physician's choice treatment
- Blood draw for pharmacokinetic testing (selinexor group only) on Day 1 of each cycle only
- Blood draw for correlative studies using peripheral blasts (Day 1 Cycle 2 only)
- AEs
- Concomitant medication assessments
- Quality of Life (FACT-Leu and EQ-5D-5L) questionnaires will be filled out on Day 1 of Cycles 2-5
- Review of temperature diary

9.2.6. Visits 9 and 11 (Day 8 and 22 of each Cycle 2 Only; Return to the Clinic

Study procedures will be performed on Day 8 and Day 22 (± 2 days) of Cycle 2, as specified in Table 1:

- Vital signs (blood pressure, heart rate, body temperature)
- Complete serum chemistry (only if fever and suspected infection are present)
- Hematology (CBC with differential)(only if fever and suspected infection are present)
- Selinexor dosing or physician's choice treatment
- AEs
- Concomitant medication assessments
- Review of temperature diary

9.2.7. Visit 18 + (Day 1 of each Cycle - Cycles ≥ 6); Return to the Clinic

Study procedures will be performed on Day 1 (± 2 days) of each cycle, as specified in Table 1:

- Symptom-directed physical examination
- ECOG Performance Status
- Body Surface Area (BSA)
- Weight
- Vital signs (blood pressure, heart rate, body temperature
- Oxygen saturation [Pulse Oximetry])
- 12-lead electrocardiogram (ECG)
- Urine dipstick
- Limited serum chemistry

- Coagulation parameters
- Hematology (CBC with differential)
- Bone Marrow Aspirate (or Biopsy if aspirate is not adequate) for disease status assessment as specified in Section 10.13
- Selinexor dosing or physician's choice treatment
- Blood draw for pharmacokinetic testing (selinexor arm only) on Day 1 only
- AEs
- Concomitant medication assessments
- Quality of Life (FACT-Leu and EQ-5D-5L) questionnaires
- Review of temperature diary

9.2.8. Final Visit (within 30 Days after last dose of study medication); Return to the Clinic

Study procedures will be performed 30 days (± 7) after the last dose of study medication for all patients, including early termination patients, as specified in Table 1:

- Complete physical examination
- ECOG Performance Status
- Full ophthalmic examination (See Appendix 3 for a detailed description).
- Weight
- Vital signs (blood pressure, heart rate, body temperature
- Oxygen saturation [Pulse Oximetry])
- 12-lead electrocardiogram (ECG)
- Urine dipstick
- Complete serum chemistry
- Hematology (CBC with differential)
- AEs
- Concomitant medication assessments
- Quality of Life (FACT-Leu and EQ-5D-5L) questionnaires
- Review of temperature diary
- Information on any antineoplastic therapies utilized since discontinuation of selinexor or PC study treatment

9.2.9. 30-Day Patient Safety Follow-up (within 30 Days after the final study visit ± 7 days); Return to the Clinic, if possible

During this patient contact either in the clinic or by phone, the most important information to be obtained includes:

- Overall medical condition of the patient and status of his/her AML
- Follow-up on any AEs that were not resolved at the Final Study Visit
- Information on any antineoplastic therapies utilized since discontinuation of study treatment

For patients who are lost to follow-up, the investigator should show 'due-diligence' by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

9.2.10. Survival Follow-up

After study discontinuation, a call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's AML status, well-being, and information on any antineoplastic therapies utilized since discontinuation of study treatment. If the patient has died, the patient's date of death will be collected, together with the reason for death, if possible.

9.2.11. Restrictions and Precautions

Alcohol: Ethanol should be avoided on selinexor dosing days as it may compete for glutathione mediated metabolism.

Fasting: Patients on the selinexor arm should maintain an adequate diet.

Medications: Acetaminophen on days of selinexor dosing will not exceed a total daily dose of 1 gram. Acetaminophen use on other days is not restricted (see Section 12.3.4).

Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. Please see Appendix 6 for a list of representative products.

Diet: There are no dietary restrictions on this study. Patients on the selinexor arm should maintain adequate caloric and fluid intake.

10. METHODS OF ASSESSMENT AND ENDPOINTS

10.1. Demographic Data

At Visit 1 (Screening #1), patient demographic data will be collected. These include year of birth, age, gender, race, and AML disease parameters.

10.2. Medical History

At Visit 1 (Screening #1), a complete medical history will be obtained from each patient. Medical history includes baseline symptoms as well as a detailed history of prior procedures and prior cancer therapies including start and stop dates, best response, disease progression during or after therapy, as well as discontinuations due to intolerability or toxicity. Smoking history will be recorded. Data will be reviewed at Visit 2 (baseline) and updated at subsequent visits.

10.3. Concomitant Medications

A detailed history of medications will be documented for each patient at Visit 1 (Screening #1), Visit 2 (Screening #2) and Visit 3 (Day 1, Cycle 1 baseline). Concomitant medications (especially changes in medication) will be documented for each patient at each scheduled visit. Necessary supportive care such as anti-emetics and anti-diarrheals etc., will be allowed (see Section 12.3.2).

10.4. Physical Examination and ECOG Score

Full physical examination evaluations at Screening #2 and the Final Study Visit should include general appearance, dermatologic, head, eyes, ears, nose, throat, respiratory, cardiovascular, abdominal, lymph nodes, musculoskeletal, and neurological examinations. Subsequent symptom-directed targeted physical exams should include body systems as appropriate.

All physical exams will include:

- Height in centimeters (cm) will be measured at Visit 2 (Screening #2) only.
- Body weight in kilogram (kg) will be measured at Screening #2 and at each visit.
- Body temperature will be measured at each visit.
- Systolic and diastolic blood pressure (BP) and pulse rate will be measured at each visit after the patient has been in a supine or sitting position for 5 minutes. Blood pressure should be assessed on the same arm at each visit during the study, if possible.

Information about the physical examination must be present in the source documentation at the study site. Clinically relevant findings made after the start of study drug, which meet the definition of an AE, must be recorded on the AE CRF.

10.5. Safety Assessments

Safety evaluations will be conducted at Cycle 1, Day 1 baseline, on Day 1 of each week for Cycle 1, Days 1 and 15 (± 2 days) for Cycles 2-5, Day 1 (± 2 days) for Cycle ≥ 6, and at the Final Study Visit. These evaluations will include a physical examination and ECOG score assessment, and a 12-lead ECG.

A full ophthalmic examination will be conducted on all patients by an optometrist or ophthalmologist at screening, at the Final Visit, and at other visits if clinically indicated. The full ophthalmic assessment includes 1) *prior to dilation*: best corrected visual acuity and slit lamp examination including tonometry and 2) *following dilation*: fundoscopy and a slit lamp exam to document lens clarity. If a cataract is seen during the examination for newly enrolling patients or enrolled patients for whom no cataracts have been detected to date, the cataract will be graded using a Grade 1-4 scale (Appendix 3). However, patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the Grade 1-4 scale.

The following clinical laboratory tests will be performed:

- **Hematology** (blood sample: EDTA) – hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.

- **Serum Chemistry** (blood sample: serum)

    - Complete Serum Chemistry for baseline, Cycles 1 Weeks 1, 2, 3, and 4, and at the Final Study Visit including sodium, potassium, chloride, bicarbonate, BUN or urea, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, LDH, total protein, albumin, pancreatic amylase, lipase, creatine kinase, TSH, and uric acid.

    - Limited Serum Chemistry for Days 1 and 15 of Cycles 2 through 5 and Day 1 of Cycles ≥ 6 including sodium, potassium, chloride, bicarbonate, BUN or urea, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, TSH, and LDH.

    - If the total bilirubin concentration is increased above 1.5 times the upper normal limit, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

- **Coagulation** – prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT). Coagulation may also be measured using thromboplastin time (Quick test) if measurement of PT/PTT is not feasible.

- **Urinalysis** – appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, urobilinogen. Microscopy will only be performed if clinically indicated.

Blood chemistry will be analyzed at each trial center by a certified laboratory and a report of the laboratory values will be sent to the trial center. The investigator or designee will review the laboratory report after receipt of the results and assess the clinical significance of all abnormal values. Results must be reviewed prior to dosing and appropriate action taken for any clinically significant abnormal values. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study medication) or baseline. Any laboratory value that remains abnormal at the Final Visit and that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline.

Toxicity will assessed using the NCI CTCAE, V4.03.

10.6. Pharmacokinetic Procedures

10.6.1. Blood Sampling and Processing

PK sampling will be done for patients in selinexor group only. Blood draws (2 mL) for PK analysis will be performed at the following times relative to in-clinic selinexor dose:

CYCLE 1

- Day 1: 0 (predose), 1, 2, and 4* hours post-dose (± 10 min for each time point)
- Day 8: 0 (predose) and 1 hour post-dose (± 10 min)
- Day 15: 0 (predose) and 1 hour post-dose (± 10 min)
- Day 22: 0 (predose) and 1 hour post-dose (± 10 min)

CYCLE ≥ 2

- Day 1: 0 (predose), 1, and 2* hours post-dose (± 10 min for each time point)

*If possible, an additional blood sample will be collected just prior to patient discharge from the clinic on Day 1 of Cycles 1-5, provided discharge time is at least 1 hour after collection of the previous sample. This sample will be labeled "pre-discharge Day 1;" the time of blood collection will be recorded in the study data. Please see Table 4 for details of blood sample collection.

If a clinic visit intended to include PK sampling occurs on a non-dosing day, PK sampling for that visit will not be done.

10.7. Pharmacokinetic Endpoints

Plasma samples will be analyzed via a validated HPLC/MS-MS method for plasma selinexor. Selinexor concentration data will be analyzed in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, and concomitant medications. CCI [redacted]

Details of the population PK analysis, including software, post-processing and statistical

analysis, will be outlined in a separate Data Analysis Plan to be completed prior to database lock.

Interim analysis may be conducted on draft plasma selinexor concentration data throughout the study. Summary statistics, including mean, median, standard deviation, coefficient of variation, and group size, may be compiled and reported during the study. Interim analysis of key selinexor PK parameters CCI [redacted].

CCI [redacted]

CCI [redacted]

CCI [redacted]

10.10. Correlative Procedures

A portion of the bone marrow aspirates and peripheral blood collected at screening and Cycle 2 Day 1 will be used for correlative studies.

10.11. Correlative Endpoints

Bone marrow aspirates: Correlative studies may include quantitative assessment of XPO1 direct targets involved in tumorogenesis (e.g., FLT3, KIT, BTK, MYC, BCl2), global µRNA

expression profiling and Next Generation Sequencing (NGS) of tumor cell DNA. Bone marrow aspirate specimens will be interrogated before and after initiation of therapy wherever feasible. Normal cells will not be interrogated and normal cell DNA will not be sequenced at this time. In bone marrow aspirate samples, preliminary correlations between molecular changes and response, along with changes when responders begin to show progression, will be made. These summaries are not meant to be comprehensive but rather provide a high level overview of the correlative research undertaken here. Additional information is found in the Laboratory Manual.

CCI [redacted]

10.12. blood Collection for PK, PD AND CORRELATIVE STUDIES

Table 4: Blood Collection Time Points and Volumes for PK, PD and Correlative Studies

TIME POINT	TOTAL VOLUME OF BLOOD (mL)	NUMBER OF TUBES BY VOLUME OF BLOOD			
		PK 1 tube x 2 mL	CCI	CCI	CCI
Screening					
Within 7 days prior to start of therapy	5				
Cycle 1, Day 1					
Pre-dose (within 10 min before dosing)	9	1 x 2 mL			
1 hr (± 10 min) post dose	2	1 x 2 mL			
2 hr (± 10 min) post dose	2	1 x 2 mL			
4 hr (± 10 min) post dose	9	1 x 2 mL			
Pre-Discharge	2	1 x 2 mL*			
Cycle 1, Day 8					
Pre-dose (within 10 min before dosing)	2	1 x 2 mL			
1 hr (± 10 min) post dose	2	1 x 2 mL			
Cycle 1, Day 15					
Pre-dose (within 10 min before dosing)	2	1 x 2 mL			
1 hr (±10 min) post dose	2	1 x 2 mL			
Cycle 1, Day 22					
Pre-dose (within 10 min before dosing)	2	1 x 2 mL			
1 hr (±10 min) post dose	2	1 x 2 mL			
Cycle ≥2, Day 1					
Pre-dose (within 10 min before dosing)	7	1 x 2 mL			
1 hr (±10 min) post dose	2	1 x 2 mL			
2 hr (±10 min) post dose	2	1 x 2 mL			
Pre-Discharge	2	1 x 2 mL*			

* If possible, sample will be collected just prior to patient discharge from the clinic on Day 1 Cycles 1-5, provided discharge time is at least 1 hour after collection of the previous sample.
† Both sampling time points are required for Selinexor group; only one sample, collected at any time during the visit, is required for the PC group.

10.13. Efficacy Procedures

Disease status will be measured by bone marrow aspirate (or biopsy if an aspirate is not adequate) at Screening and on Day 1 of Cycle 2, and as clinically indicated to assess treatment response. CCI [redacted] If the patient has achieved CR, bone marrow (BM) aspirates/biopsies are not required unless clinically indicated. For patients with circulating blasts in peripheral blood, there is no need to perform the bone marrow aspirates and biopsies for Cycles > 2. For patients without circulating blasts that achieved a PR or SD, bone marrow aspirates/biopsies will be conducted every other cycle until CR/CRi is achieved, or until progression.

Disease response assessment will be made according to the International Working Group (IWG) criteria (Cheson 2003; Appendix 2).

10.14. Efficacy Endpoints

Overall survival (OS) is the primary efficacy endpoint of this study.

Secondary efficacy endpoints will include the following, assessed in hierarchical fashion in the order presented below:

- The proportion of patients whose OS is at least 3 months (OS3.0)
- The complete remission rate (CRR), including complete remission with full hematologic recovery (CR), and median disease free survival (DFS) for patients who achieve CR
- The modified CRR (mCRR), including CR or CRi (including CRp), and median DFS for patients who achieve CR or CRi (including CRp)
- The overall response rate (ORR) and duration of overall response (DOR), including CR, CRi, MLFS, and partial remission (PR)
- To determine the disease control rate (DCR) defined as ORR + stable disease for ≥ 4 weeks (SD), and duration of DCR
- Quality of life and patient reported outcomes (FACT-Leukemia and EQ-5D-5L) (QoL)

11. DISCONTINUATION CRITERIA

11.1. Early Discontinuation of the Study

The study may be discontinued at the sole discretion of the sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients. The results of the two interim analyses, to take place after approximately one- quarter and one-half the required number of OS events have occurred, may result in a statistical conclusion of futility (see Section 14.1.2), and this would be taken into consideration in the decision to potentially stop the trial. Note also that a sample size re-assessment may also be performed at the second interim analysis, in order to maintain sufficient conditional power (see Section 14.1.2).

11.2. Early Discontinuation of Individual Patients

At the discretion of the investigator, the investigator may remove a patient from study treatment for the following reasons:

- Disease progression defined as an increase in blast counts and absence of hematologic recovery (one or more lineages)
- Unacceptable adverse event(s) or failure to tolerate the study treatment
- Patient decides to discontinue study therapy
- Significant deviation from entry criteria (e.g., non-relapsed or non-refractory AML)
- Misuse of study medication (e.g., deliberate overdosing by patient)
- Missed/unscheduled/off-schedule/incomplete/incorrect assessments that result in patients being put at risk
- Any other medically appropriate reason or significant protocol violation, in the opinion of the investigator.

The investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the eCRF. Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment at a later date.

Patients may decide to discontinue study treatment for any reason. Patients who elect not to initiate study treatment or to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial.

Patients will be followed for survival until the last patient has been followed for 6 months from the end of treatment, disease progression, another withdrawal criterion is met, or until death, whichever comes first.

11.3. End of Study

End of study (Last Patient Last Visit) will be upon completion of the follow up period for the last patient treated in the study. Completion of follow-up will occur when the last patient in

the study has expired, has been followed for 6 months after the end of treatment, has been lost to follow-up, or has withdrawn consent, whichever occurs first.

12. TREATMENT

Selinexor study medication will be in the form of a coated, immediate release tablet for oral administration. Selinexor tablets will be supplied in bottles or blister packs. Tablets in bottles will be provided in two coated tablet strengths: 10 and 25 mg. Study medication of 50 tablets per bottle will be supplied for each of the two strengths. Tablets in blister packs will be provided in a coated tablet strength of 20 mg.

The study sites will use their own supply of physician's choice (PC) study medication, as per agreement with the site contract with Karyopharm.

12.1. Dosing and Administration of Physician's Choice Study Medication (Reference Therapy)

Based on the patient's performance status, organ function, and comorbid conditions, one of the following three conventional care regimens will be selected by the treating physician: (1) best supportive care (BSC) including blood product transfusions, antimicrobials, growth factors as needed, and hydroxyurea; or (2) BSC + low dose AraC, 20 mg bid by subcutaneous (sc) injection daily on Days 1-10/14 (20/28 doses) to be repeated at 28 to 42 day intervals; or (3) BSC + hypomethylating agent: azacitidine 75 mg/m^2 by sc injection daily on Days 1-7 or 1-5, 8-9 (7 doses) to be repeated at ≥28 day intervals, *or* decitabine (20 mg/m^2 IV over 1 hour daily on days 1-5 or days 1-10 to be repeated at ≥ 28 day intervals).

12.2. Dosing and Administration of Selinexor

12.2.1. Labelling

Selinexor tablets will be labeled in accordance with current International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and specific national requirements. Medication labels will comply with local language and legal requirements of each country. Labels will include storage conditions.

12.2.2. Dispensing Directions

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug will be dispensed to the patient by authorized site personnel only.

12.2.3. Dosing Information

Selinexor will be initiated at a fixed oral dose of 60 mg (equivalent to ~35 mg/m^2 mg/m^2) twice weekly (e.g., Monday and Wednesday or Tuesday and Thursday or Wednesday and Friday). Patients who were randomized to selinexor (~55 mg/m^2) under Protocol Versions < 5.0 will be switched to the 60 mg fixed dose.

In order to minimize nausea and vomiting, it is recommended that selinexor tablets be taken within 30-minutes of food consumption together with at least 120 mL (4 ounces) of fluids.

12.2.4. Dosing Instructions for the Study Participants

Selinexor dosing will occur on Day 1 and Day 3 of each week of a four week 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. Compliance to study medication will be done by the investigator or delegate and recorded in source documents. The date will be recorded as per study drug schedule. The principal investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the CRF and drug accountability logs for verification with the reasons. The investigator / designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients.

12.3. Dose Reduction and Supportive Care Guidelines

12.3.1. Dose Modifications and Dose Delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The criteria for dose modifications for toxicities considered at least possibly related to the study medication treatment are outlined in Table 5 and Table 6. These changes must be recorded on the eCRF. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study. (In exceptional situations, if the patient is clearly benefiting from the study treatment, and in the opinion of the investigator no safety concerns are present, after discussion with Karyopharm, the patient may remain in the study.) Re-escalation of the study drug is allowed as outlined in the sections that apply for the specific toxicity. Patients who discontinue from the study for a study-related AE or an abnormal laboratory value must be followed as described in Section 11.2. All interruptions or changes to study drug administration must be recorded on the eCRF.

Toxicity will be graded according to NCI CTCAE, V 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.

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 activity at doses from ~10 mg/m^2 to ≥ 50 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.

Table 5: Prespecified Dose/Schedule Modifications for Adverse Events Related to Study Drug

Dose Level	Dose of Selinexor
Dose level 0	60 mg twice weekly (Day 1, Day 3)
Dose level -1	40 mg, twice weekly (Day 1, Day 3)
Dose level -2	20 mg, twice weekly (Day 1, Day 3)
Dose level -3	20 mg, once weekly (Day1)
Dose level -4	Discontinue Dosing

Table 6 contains supportive care and selinexor dose adjustment guidelines for non-hematologic selinexor-related toxicities. Additional supportive care guidance can be found in Section 12.3.2.

Table 6: 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.	Maintain dose.
Grade 2	Rule out other causes of fatigue. Insure adequate caloric intake and assess volume status. Supportive care for fatigue per institutional guidelines and recommendations in NCCN guidelines: Fatigue[a.]	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 (Table 5).

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
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®). Strongly encourage a low dose appetite stimulating agent (e.g., megesterol acetate 40-80 mg bid, up to 200 mg bid daily)	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®). Strongly encourage megesterol acetate 40-80 mg bid, up to 200 mg bid daily. Strongly encourage anabolic steroids such as oxandrolone, or dronabinol (Marinol®) or other cannabinoid. For additional supportive care see NCCN guidelines[b] (Appendix 5).	Selinexor may be skipped intermittently while supportive medications are instituted, usually for < 1 week.
Grade 3	See guidelines for Grade 2 anorexia.	Interrupt dosing with selinexor. Restart selinexor at 1 dose level reduction (Table 5) 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 (Table 5) 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.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 2	See guidelines for Grade 1 nausea. For additional options see NCCN guidelines for antiemesis[c] (Appendix 4).	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[c] (Appendix 4).	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 (Table 5). If nausea stabilizes for at least 4 weeks at Grade ≤ 1, then original dose of selinexor may be resumed.
Hyponatremia (common)		
Grade 1 (sodium levels <Normal to 130 nM)	Be certain sodium level is corrected for hyperglycemia (serum glucose > 150 mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Consider salt supplementation one – two times per day.	Maintain dose.
Grade 3 (sodium levels 126-129 nM) without Symptoms	Be certain sodium level is corrected for hyperglycemia (serum glucose > 150 mmol/L). Rule out other causes of low sodium (e.g., cardiac, hepatic, adrenal, renal and thyroid diseases, SIADH, Fanconi Syndrome, hyperglycemia, diuretic use). Initiate salt supplementation two-three times per day.	Hold selinexor until Grade ≤ 1 (≥ 130 nM), restart on the same dose level.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
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 (Table 5) 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 2004[d] 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 (Table 5) until resolved to ≤ Grade 1, then re-start at the current dose level.
Grade 3	Institute IV fluids Diet recommendation as per Benson 2004[d] 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 (Table 5) 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 (Table 5).
Other selinexor-related adverse events*		
Grade 1 or 2	Initiate standard supportive care and follow institutional guidelines.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
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 (Table 5).
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 (Table 5).
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.		
[a]**National Comprehensive Cancer Network®**. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Fatigue. Available at: http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf [b]**National Comprehensive Cancer Network®**. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Palliative Care, version 1.2014. Fort Washington, NY. April 2014. Available at: http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf. [c]**National Comprehensive Cancer Network®**. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, version 2.2014. Fort Washington, NY. April 2014. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. [d]Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Onc 2004; 22:2918.		

For all ≥ Grade 3 hematological or non-hematological AEs that are NOT selinexor-related:

After consultation with the Medical Monitor and at the discretion of the treating physician, selinexor dosing may be maintained provided that the patient can continue to take the agent by mouth, or via other enteral route.

12.3.1.1. Selinexor Dose Adjustments for Hematological Toxicities

No dose adjustments or treatment interruptions for myelosuppression are required in the presence of residual leukemia. Treatment may be continued regardless of neutrophil and platelet count, with supportive care (e.g., transfusions) provided as needed. Treatment interruptions and dose adjustments may be considered according to the following guidelines only when there is no evidence of active leukemia (e.g., only if < 5% blasts in the bone marrow or cytopenias not considered to be related to leukemia).

- Patients with a response (e.g., only if < 5% blasts in the bone marrow or cytopenias not considered to be related to leukemia) and pre-cycle counts of neutrophils > 1x 10^9/L and platelets > 50 x 10^9/L who have sustained low counts of neutrophils < 0.5 x 10^9/L or a platelet count < 20 x 10^9/L for more than 2 consecutive weeks in the current cycle, may

have the treatment with selinexor interrupted at the discretion of the treating physician until neutrophils recover to ≥ 1 x 10^9/L and platelets to ≥ 50 x 10^9/L.

- Patients with a response (significant reduction in marrow blast count) and pre-cycle counts of neutrophils < 1 x 10^9/L and platelets < 50 x 10^9/L may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions in these patients should be considered on an individual case and discussed with the Sponsor.

12.3.1.2. Selinexor Dose Adjustment for Decreased Glomerular Filtration Rate (GFR)

Selinexor is not significantly eliminated by the kidney. Therefore, no dose alteration of selinexor is required with renal dysfunction.

12.3.1.3. Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled infections should have selinexor treatment withheld until infection has clinically resolved or the patient is clinically stabilized. However, selinexor has not been associated with opportunistic infections in 730 patients evaluable for safety as of 31 May 2015. Therefore, after the infection has resolved clinically or the patient's clinical condition has stabilized, treatment with selinexor may continue at the original dose. Missed doses will not be replaced. Patients may continue on antibiotics for prolonged periods while re-initiating their selinexor regimen at the discretion of the investigator.

12.3.1.4. Conditions not Requiring Selinexor Dose Adjustment

The following conditions are exceptions to the above guidelines. Selinexor does not need to be held in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions

12.3.1.5. Dose Adjustments with Changes in BSA

Dose adjustments do not need to be made for weight losses of ≤ 20%. If a patient dose will exceed the maximum allowable dose of 70 mg/m^2, the Investigator should contact the medical monitor prior to administration to discuss appropriate dosing.

12.3.1.6. Missed or Vomited Doses

12.3.1.6.1. Missed Doses

A maximum of two doses may be given per week. Doses should not be administered in less than 36 hrs apart and all missed doses should be documented. Every effort should be made to avoid missed doses.

If a patient missed a full week of dosing (e.g., a required medical procedure or an unanticipated personal emergency), the days missed will not be replaced. For example, if patient missed Cycle 2 Day 7 to Cycle 2 Day 14, then patient will start on Cycle 2 Day 15.

12.3.1.6.2. 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. For example, if patient missed Cycle 2 Day 7 to Cycle 2 Day 14, then patient will start on Cycle 2 Day 15.

12.3.2. Supportive Care and Concomitant Treatments

12.3.2.1. Required Supportive Care Medications

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).

12.3.2.2. 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 730 adult patients treated with selinexor with evaluable safety data as of 31 May 2015, 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 5-HT3, aggressive use of other supportive care including anti-nausea / anti-emetic therapy, acid suppression (proton pump inhibitors and/or H2-blockers) and other treatments as described below is strongly recommended:

1. Appetite stimulants: megesterol acetate at a starting dose of 40-160 mg bid, up to 200 mg bid daily. Aggressive and early use of appetite stimulants such as megesterol acetate is strongly recommended in any patient with selinexor-associated anorexia; these can often be tapered after the first 2-3 cycles of therapy.
2. Centrally acting agents: per National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines® for antiemesis and anorexia/cachexia [palliative care]) see (antiemesis) and Appendix 5 (anorexia), respectively.
3. NK1R antagonist: aprepitant or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.
4. Supportive care for fatigue per institutional guidelines and NCCN guidelines: Fatigue (NCCN Guidelines for Fatigue).

Additional information on supportive care and dose modifications for specific adverse events can be found in Table 6.

12.3.2.3. Infection

Patients with relapsed AML are at risk for developing serious infections (bacterial, invasive fungal disease). Prophylactic antimicrobials are strongly encouraged for patients with pre-

cycle absolute neutrophil counts < 1 x 10^9/L, particularly if the neutropenia is prolonged. Appropriate broad-spectrum intravenous antibiotics and antifungal agents should be started immediately in patients who develop fever or other signs of systemic infection. Selinexor should be suspended in any patient with Grade 4 infection or clinical sepsis (in the absence of documented infection) until the condition is stabilized. Selinexor can then be re-started at the same dose.

12.3.3. 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). All concomitant medication(s) must be reported in the case report form (CRF). 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.

12.3.3.1. Permitted Concomitant Medication

Patients will receive concomitant medications to treat symptoms, adverse events and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc. are allowed. Acetaminophen on days of selinexor dosing is permitted but will not exceed a total daily dose of 1 gram.

Hydroxyurea may be used at any time during the study, typically in patients with WBC ≥ 30,000/μL or per institutional guidelines. Prior to the initiation of hydroxyurea please consider the contraindications in the SPC, including leukocytopenia (< 2.5 x 10^9 leukocytes/L), thrombocytopenia (< 100 x 10^9 platelets/L) or severe anemia.

12.3.3.1.1. 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 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.

12.3.3.1.2. Use of Blood Products

During the administration of selinexor, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Patients who require repeated transfusion support should be discussed with the PI, Sponsor and Medical Monitor.

Appropriate anti-coagulation is allowed during the study (e.g., low molecular weight [LMW] heparin, direct factor Xa inhibitors, etc.). Warfarin is allowed during the study provided that patients are monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly thereafter.

Patients may receive supportive care with erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF), pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

12.3.3.1.3. Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study drug should be held for 3-5 days before the start of palliative radiation therapy and 3-5 days after palliative radiation therapy. Treatment with selinexor shall not be discontinued solely due to palliative radiation.

12.3.4. Prohibited Medication

Concurrent therapies: Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed in either arm. 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: *Acetaminophen* There are no longer any restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days on selinexor dosing, when acetaminophen must not exceed a total daily dose of 1 gram.

Glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products Patients should not take GSH-, SAM-, or NAC-containing products during their participation in this study as these products may enhance the metabolism of selinexor. Please see Appendix 6 for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

12.4. Selinexor Storage and Accountability

Selinexor tablets will be stored at ambient or refrigerated temperatures between (41-86°F) or (5-30°C) in a locked and secured area with restricted access to study staff. The tablets should not be stored at freezer temperatures or allowed to freeze. Tablets will be supplied in white high density polyethylene (HDPE) bottles. 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).

Selinexor for the study will be provided by Karyopharm Therapeutics, Inc. Medication labels will comply with the legal requirements of each country and will be printed in the local language as required. The investigator (or designee) will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

Study drug accountability records will be maintained at the site pharmacy and will be available for review by the study monitor during each monitoring visit and at the close out visit. The study drug must be reviewed by the clinical research associate (CRA) prior to destruction or return shipment.

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. Data for Investigational medicinal product are confidential and proprietary and shall be maintained as such by the investigators.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of unused material.

All selinexor tablets must be kept in an appropriate, limited access, secure place until used or returned to Karyopharm Therapeutics, Inc. or designee for destruction. Drug supplies will be counted and reconciled at the site before being returned. The study site will be required to maintain a log of the temperature where the study medication is stored

12.5. Treatment Compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the source documentation. This information must be captured in the source document at each patient visit. The respective dose for investigational drug and any changes in dosing must be captured in the eCRF. Additionally, the exact time and date of dosing will be captured on the days of PK sampling.

13. ADVERSE EVENTS

An adverse event (AE) is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the eCRF:

1. Accompanied by clinical symptoms

2. Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)

3. Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the responsibility of the investigator to document all AEs that occur during the study. AE information will be elicited by asking the patient a non-leading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” AEs should be reported on the appropriate page of the eCRF.

AEs should be reported for their actual grade and duration.

- The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as “serious”. Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a patient’s life or functioning.

The severity of the AE will be graded according to the NCI CTCAE Grading Scale Version 4.03 (see the NCI CTCAE web page at http://ctep.cancer.gov for details). For AEs not covered by NCI CTCAE, the severity will be characterized as “mild”, “moderate”, or “severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activities.

The investigator will make a judgment regarding whether or not the AE was related to study drug, as outlined in Table 7:

Table 7: Classification of Adverse Events by Causality

Unrelated	The adverse event is unlikely to have been caused by study drug.
Possibly related	It is unclear whether the adverse event may have been caused by study drug.
Related	The adverse event is likely to have been caused by study drug.

13.1. Serious Adverse Events, Overdose

A Serious Adverse Event (SAE) is any untoward medical occurrence that occurs at any dose (including after the Informed Consent Form [ICF] is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs.

Progression of the malignancy under study (including signs and symptoms of progression), including fatal outcomes if documented per IWG criteria, should not be reported as an SAE during the study or within the safety reporting period (see below).

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

13.1.1. AE and SAE Follow-up

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related (possibly related, related) must be followed until resolution or until stabilization. Any AE of rash should be documented until resolution with photographs.

13.1.2. Post-Study Adverse Events and Serious Adverse Events

All unresolved AEs should be followed by the investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study.

For any patient who discontinues from treatment, a Survival Follow-Up telephone call (See Table 1 and Section 9.2.10) be made by study personnel every three months to the patient (or the patient's family) to inquire about the patient's AML status, initiation of anti-neoplastic therapies, and survival status.

Prior to the conclusion of the study at the site the investigator should notify the Karyopharm Pharmacovigilance Department (see Section 13.1.5.1) of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study.

After study conclusion, the investigator should notify the Karyopharm Pharmacovigilance Department of any death or AE he or she is aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. Karyopharm Therapeutics, Inc. should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that has participated in this study.

13.1.3. Overdose

An overdose is defined as a deliberate or accidental administration of study medication to a study patient, at a dose above that which is assigned to that individual patient according to the study protocol. In the event of drug overdose, the investigator should be notified immediately and the patient observed closely for adverse effects. The patient should be treated symptomatically as appropriate, and the incident of overdose and related AEs and/or treatment documented in the patient's medical record.

As selinexor is metabolized by glutathione (GSH) conjugation it is conceivable that hepatic GSH depletion can occur in case of overdose. Therefore, in patients who develop liver function test abnormalities, supportive measures such as S-adenosylmethionine (SAM) 400 mg po qd – qid or other drugs that can replace GSH should be considered. There have been no reports of selinexor overdose in > 1000 patients treated with selinexor to date.

13.1.4. Pregnancies

Pregnancy *per se* is not considered an AE. A medical occurrence observed in the mother or fetus/newborn would be an AE.

Each pregnancy in a partner of a patient on selinexor must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. All attempts will be made to follow-up and document the course of pregnancy and birth. Follow-up and documentation must occur even if the patient withdraws from the study or the study is completed.

The avoidance of fathering a child is suggested for 3 months following the discontinuation of selinexor therapy. No information is currently available regarding the effects of selinexor on fertility, gestation or subsequent child development.

Any pregnancy within 3 months post-study should be reported to the study investigator and to the Karyopharm Pharmacovigilance Department.

13.1.5. Serious Adverse Event Reporting

13.1.5.1. Reporting Requirements

ALL SAEs and cases of overdose occurring in any patient, must be notified to Karyopharm within 24 hours of first knowledge of the event by the principal investigator or assigned site personnel. The principal investigator or assigned site personnel are requested to provide following information:

- Protocol number
- Site and/or investigator number
- Patient number
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event resolved
- Any medication administered to treat the event
- Investigator’s assessment of the SAE’s relationship to investigational product
- Outcome of the event on the date of report

This information will be captured in the protocol specific SAE report form and will be forwarded to:

Pharmacovigilance Department
Karyopharm Therapeutics Inc.
Email: pharmacovigilance@karyopharm.com
Fax: +1-617-3347-617 (US)
+49-89-9218-5650 (Germany)

Karyopharm Therapeutics Inc. is responsible for submitting reports of AEs associated with the use of the study medication that are both serious and unexpected in compliance with the ICH Harmonized Tripartite Guidelines, to the regulatory agencies of the countries where this trial is being conducted, in accordance to country specific regulations.

All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Ethics committee (EC), as applicable. Reporting of SAEs by the investigator to the IRB or EC will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

In addition, all cases of cerebellar toxicities of Grade 3 or higher must be captured as an SAE and reported to the regulatory authorities, IRBs, ECs and investigators in an expedited Safety Report within 7 days of awareness of the event.

14. STATISTICAL METHODS

14.1. General Considerations

14.1.1. Statistical and Analytical Plans

This is a randomized, multicenter, open-label phase 2 study of the SINE compound selinexor given orally versus investigator choice (one of three potential salvage therapies) in heavily pretreated, transplant ineligible patients of age ≥ 60 years, with relapsed/refractory AML. Formal hypothesis testing methods will be used for efficacy endpoint data, in order to evaluate if selinexor provides statistically significant improvement in efficacy over the control agents (collectively) used in this study. No formal hypothesis-testing will be used for other study data, such as demographics and safety data.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals (CI), unless otherwise stated. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

14.1.2. Determination of Sample Size

Patients enrolled under Protocol Versions < 5.0 will not be included in the efficacy analyses; therefore, sample size justification will refer to patients to be enrolled under Protocol Versions ≥ 5.0.

The sample size is designed to have 80% power to detect a median OS for patients treated with selinexor of ~5.2 months, versus investigator choice of ~3.0 months, using a one-sided alpha of 0.025 and allowing for two interim analyses. The follow up period for survival is up to 6 months after the end of treatment for the last enrolled patient for the primary analysis, and a ~20% drop out rate is assumed. Based on these statistical assumptions, a total of 123 events (deaths) are required for analysis. To achieve these events, a total of approximately 169 patients are required for enrollment; in order to maintain the 2:1 randomization allocation to selinexor:PC, this number is rounded up to 171 patients. Therefore, a total of approximately 171 patients with relapsed or refractory AML will be enrolled into the study from approximately 60 sites in North America, Europe and the rest of the world. Patients will be randomized into the selinexor or PC treatment arms in a 2:1 allocation, within each of the 2 x 2 x 2 stratification levels noted in Study Design.

As described in Section 4.3.1.1, following a thorough evaluation of patient safety from the first approximately 110 patients enrolled under Protocol Versions < 5.0, a dose reduction for selinexor is being implemented. Under Protocol Versions < 5.0, the selinexor group was prescribed a dose equivalent to ~55 mg/m^2 based on the patient's BSA twice weekly. Under Protocol Versions ≥ 5.0, the selinexor group will receive a fixed dose of 60 mg (equivalent to ~35 mg/m^2) twice weekly. Patients enrolled under Protocol Versions < 5.0 will not be included

in efficacy analysis. The total sample size of the study is expected to be approximately 300, as approximately 110 patients were enrolled under Protocol Versions < 5.0; enrollment will continue until Protocol Version 5.0 is approved.

Two interim efficacy analyses are planned for patients enrolled under Protocol Versions ≥ 5.0 as noted in Section 14.2.1.4.

14.1.3. Disposition of Patients

A tabulation of patient disposition will be presented, including the number in each analysis population, the number with non-evaluable disease according to the International Working Group (IWG) classic criteria, the number in each analysis population, the number censored at each of the PFS and OS analyses, the number lost to follow-up, the number that withdrew and reason(s) for withdrawal.

A by-patient listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

14.1.4. Blinding and Randomization

Study drug will be administered in a non-blinded manner. Randomization will be performed centrally using an Interactive Web Response System (IWRS), and patients will be randomized with a 2:1 allocation to receive selinexor or control. The randomization will be stratified by (1) duration of their first CR on prior therapy, ≤ 6 months (including no CR on prior therapy) versus > 6 months; (2) number of prior therapies, 1 versus >1; (3) peripheral leukemic blast counts ≥ 10,000/μL versus < 10,000/μL. The randomization process will maintain the 2:1 allocation between treatment groups within each of the stratification categories.

The total number of patients enrolled within a randomization stratum will not be restricted overall or by site.

14.2. Analysis Datasets

14.2.1. Population to be Analyzed

14.2.1.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all patients who are randomized to study therapy under Protocol Versions ≥ 5.0. Patients randomized under Protocol Versions < 5.0 will not be included for efficacy analyses. This population will include patients who have discontinued therapy due to toxicity or disease progression and patients who have died from any cause. This population will be used for primary analyses of efficacy, and such analyses will be based on the randomized treatment assignment.

14.2.1.2. Per Protocol Population

The per-protocol (PP) population will consist of all patients randomized to study therapy under Protocol Versions ≥ 5.0 who have been administered at least 2 months of study drug treatment, who are compliant with study assessments and have received at least 80% of their prescribed study medication, and who have no major protocol violations that would compromise the assessment of efficacy. Major violations will be determined independently of knowledge of

response to therapy. This population will be used for supportive inferences concerning efficacy; however, if there are major differences between the results in this population and those obtained in the ITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.

14.2.1.3. Safety Population

The safety population will consist of all patients who have received any amount of study medication; analyses of safety will be performed based on treatment received, even if different from that randomized. Patients enrolled under all protocol versions will be included in the safety population.

14.2.1.4. Interim Analyses

Two interim efficacy analyses will be conducted on patients meeting the criteria to be included in the ITT population. The first interim analysis will take place after 31 (25%) OS events have occurred, and will be conducted to assess futility only (non-binding). Futility would be concluded if the p-value from the log-rank test is $\geq$0.8084. The second interim analysis will take place after 62 (50%) OS events, and will allow for a conclusion of significant efficacy at an α-level < 0.0015, and stopping for futility (non-binding) at an α-level ≥ 0.2957. The Sponsor may elect to continue the study even if the second interim analysis of OS demonstrates a p-value < 0.0015, in order to provide further safety data or to more fully explore secondary endpoints. The final hypothesis test will be performed after 123 OS events are observed with a one-sided significance level of 0.0245. Type I error adjustments were made using the O'Brien-Fleming approach. At the second interim analysis, a sample size re-assessment will be performed if the study is not stopped for futility, and significant superiority is not claimed. Sample size re-assessment would therefore only be performed conditionally on log-rank test results where $0.0015 \leq p < 0.2957$, therefore alpha control is maintained. The sample size may be increased in order to ensure a minimum of 80% conditional power, where conditional power is calculated as the probability of a statistically significant result from the stratified log-rank test at the final analysis, conditional on the result at the interim. Complete details of the sample size re-assessment method are contained in the statistical analysis plan for this study.

The statistical analyses of interim efficacy to determine a recommendation to stop the trial for significant efficacy or futility will be performed by the DSMB statistician, based on data provided to the DSMB by the biometrics CRO. The recommendation to stop or continue the trial will be provided to the Sponsor by the DSMB, after a thorough review of the efficacy results, in conjunction with an overall evaluation of safety.

In addition to the interim analyses performed on the ITT population, a review of safety data for all patients will also be conducted at each interim analysis.

14.3. Data Analysis and Presentation

Summary tabulations will be provided for disposition as noted above, and for demographic, baseline, efficacy and safety data as noted in the following sections. All data collected on the electronic case report form (eCRF) will be provided in by-patient data listings. The primary presentation of all non-efficacy data will use a 4 treatment arm classification of: selinexor at the 2 dose levels of ~55 mg/m^2 (Protocol Versions < 5.0) and 60 mg (35 mg/m^2) (Protocol

Versions ≥ 5.0), control group 1 (Protocol Versions < 5.0) and control group 2 (Protocol Versions ≥ 5.0), where "control" is meant to designate including all 3 PC therapies together. CCI

14.3.1. Demographic Characteristics

Demographic characteristics will be summarized by treatment arm, and will include gender, race, ethnicity (Hispanic origin), and age at time of consent. For gender, race, and Hispanic origin, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample.

No formal hypothesis testing of treatment arm differences will be performed.

14.3.2. Baseline Characteristics and Medical History

Baseline characteristics include Performance Status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and history of stem cell transplant. Baseline data will be summarized for each treatment arm using summary statistics; no formal hypothesis testing of treatment arm differences will be performed.

Medical history and physical examination results at baseline will be tabulated by treatment arm.

14.3.3. Primary Endpoint

Patients enrolled under Protocol Versions < 5.0 will not be included in the efficacy analyses described below. Efficacy data from these patients will be tabulated separately from the data of patients enrolled under Protocol Versions ≥ 5.0 and no formal statistical hypothesis testing will be performed on the prior efficacy data. Therefore, references to efficacy analysis will be intended for the data collected from patients enrolled under Protocol Versions ≥ 5.0.

For patients meeting the criteria to be included in the ITT or PP populations, OS will be calculated from the date of randomization to the date of death. Patients who are still alive at the time point of analyses, or who drop out prior to study end, will be censored at the day they were last known to be alive. The statistical significance of the treatment group difference in OS will be based on the stratified log-rank test, using the strata included for randomization. The median duration of OS will be estimated based on the 50th percentile of the Kaplan-Meier (KM) distribution; additional summary statistics will be presented, including the 25th and 75th percentiles, 95% CIs on the median and other percentiles, and proportion of censored data. Kaplan-Meier survival rates will also be calculated.

The hazard ratio (HR) and 95% CI for treatment group difference will be estimated from a stratified Cox proportional hazards model overall adjusted for strata and within randomization strata. The adequacy of the model will be evaluated, including an assessment of the proportional hazards assumption. CCI

14.3.4. Secondary Endpoints

In order to preserve the overall Type I error for the study, secondary efficacy variables will be assessed in hierarchical fashion in the following order, using the definitions presented above (Secondary Objectives):

- OS3.0
- CRR and DFS for CRR
- mCRR and DFS for mCRR
- ORR and DOR
- DCR and duration of DCR
- QoL

The hierarchical assessment will proceed as follows, with all statistical tests performed at the one-sided, 0.025 level. OS3.0 will be assessed for statistical significance only if OS is statistically significant. Subsequent to a significant result for OS3.0, CRR will be assessed, and so forth for all remaining secondary variables, in order.

For OS3.0, the difference in survival at 3 months post-randomization will be based on the stratified KM curves, using all available data at the time of analysis.

CRR will be analyzed as the difference in the proportions of subjects with IWG results of CR and will be compared between the treatment arms, accounting for randomization strata, using a Cochran Mantel-Haenszel (CMH) chi-square test. The analysis of mCRR, ORR and DCR will be performed in a similar manner to CRR, using the CMH test.

Duration of response will be calculated for each response rate: CRR, mCRR, ORR, and DCR. The duration of response for each respective type of response will not be used in the overall hierarchy used to maintain alpha-control, but will be regarded as descriptive adjuncts to the analyses of response rates. Analysis of duration of each response type will be performed using stratified KM methods.

- For CRR and mCRR, the duration of response will be based on disease-free survival, defined as the duration from start of the complete response achieved based on IWG criteria until disease progression or death from any cause.

- For ORR, duration of response will be calculated as the duration from the date when first evidence of overall disease response was achieved until the first date of documented disease recurrence or progression. Patients without documented disease recurrence or progression will be censored at the date of last disease assessment.

- For duration of DCR, duration of response will be similar to that of ORR; however, the start of DCR will be based on the date of randomization.

QoL will be assessed using the Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) and the European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L). FACT-Leu combines the General version of the Functional Assessment of Cancer Therapy

(FACT-G) with a leukemia-specific subscale (17 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 31 items) will be the primary measurement of interest, comprised of the Physical and Functional subscales plus the leukemia-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (="Not at all") to 4 (="Very much"), therefore the TOI has a score ranging from 0 to 124. The QoL assessment will be performed at Baseline (prior to first dose of study treatment), Day 1 of each cycle on or after the second, and at the Final visit. The primary endpoint analysis will take place based on changes in the total TOI score from Baseline using mixed model repeated-measures analysis of variance (MMRM) with treatment as the factor of interest and the stratification levels as additional fixed factors. The primary inference will be drawn from this model, for change from Baseline to Final visit. A secondary analysis of QoL will be performed in a similar manner using the total of all subscales. All individual subscale total scores will be summarized over time using descriptive statistics.

The EQ-5D-5L consists of assessment of 5 health categories (5 levels each category) and overall health score ("Your Health Today" on 1-100 scale). Change from Baseline in the overall health score (EQ VAS) will be analyzed using a MMRM model, similar to the FACT-Leu TOI score as described above. All 5 individual category scores will be summarized over time using descriptive statistics

14.3.5. Pharmacokinetic Data

Plasma samples will be analyzed via a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for plasma selinexor concentration. Selinexor concentration data will be analyzed in a non-linear mixed effects population PK model with potential covariates including, but not limited to: age, body weight, gender, disease state, baseline hepatic or renal function, concomitant medications, and treatment. CCI [redacted] etails of the population PK analysis, including software, post-processing and statistical analysis, will be outlined in a separate Data Analysis Plan, to be completed prior to database lock.

Interim analysis may be conducted on draft plasma selinexor concentration data throughout the study. Summary statistics, including mean, median, standard deviation, coefficient of variation and group size may be compiled and reported during the study. Interim analysis of key selinexor PK parameters CCI [redacted]

14.3.6. Safety Data

Safety analyses will be performed on the Safety Population, including all patients who receive at least one dose of any study medication, regardless of which protocol version they were enrolled under. Summary tables will be presented by treatment group, with the selinexor group presented both overall and separately by patients enrolled under Protocol Versions < 5.0 and patients enrolled under Protocol Versions ≥ 5.0. Similarly, the safety data for the control group

patients will be presented both overall and separately by patients enrolled under Protocol Versions < 5.0 and patients enrolled under Protocol Versions ≥ 5.0.

14.3.6.1. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class (SOC) and Preferred Term.

Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment-emergent is defined as any AE with onset or worsening of a pre-existing condition on or after the first dose of randomized treatment through 30 days following the last dose of randomized treatment, or any event considered drug-related by the investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent. No formal hypothesis-testing of AE incidence rates will be performed.

AEs will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given AE (preferred term).The number and percentage of patients with any TEAE will be summarized for each treatment group, classified by SOC and preferred term. The number and percentage of patients with TEAEs assessed by the investigator as at least possibly related to treatment will also be tabulated. The number and percentage of patients with any Grade ≥ 3 treatment-emergent AE will be tabulated in the same manner.

The causal relationship between the occurrence of an AE and the study drug will be judged by the investigator as unrelated, possibly related and related. In the event a patient experiences repeat episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to treatment will be used for purposes of tabulations.

Serious adverse events (SAEs) will also be tabulated.

The incidence rates of selected treatment-emergent AEs, serious AEs, AEs of at least Grade 3 in severity, related AEs, and AEs leading to withdrawal of treatment may be analyzed for treatment group differences using Fisher's Exact test. All AEs (treatment emergent and post-treatment) will be listed in by-patient data listings, classified by treatment, patient and day on study. In addition, separate by-patient listings will be provided for the following: patient deaths; serious AEs; and AEs leading to withdrawal.

14.3.6.2. Laboratory Data

Clinical laboratory values will be expressed using conventional SI units.

For each treatment arm, the actual value and change from Baseline (Day 1, prior to the first administration of study drug) to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation and urinalysis. In the event of repeat values, the last non-missing value per study day/time will be used. In the

event that Day 1 data are unavailable for a given patient/parameter, the Screening value will substitute as the baseline value.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE grades greater than or equal to 3 will be presented in a data listing. Shift tables that present changes from Baseline to worst on-study and Baseline to last on-study values relative to CTCAE classification ranges will be produced.

14.3.6.3. Vital Signs and Physical Examinations

The actual value and change from Baseline (Day 1) to each on study evaluation will be summarized for vital signs.

By-patient listings of vital sign measurements will be presented in data listings.

Physical examination results at screening, and physical examination results changes during the study, will be summarized. All physical examination findings will be presented in by-patient data listings.

14.3.6.4. Concomitant Medications

The use of concomitant medications will be included in by-patient data listings.

14.3.7. Procedures for Handling Missing Data

No imputation of missing efficacy data is planned. For time to event analyses, patients who have no efficacy evaluations will be considered as censored at time 0. For PFS, patients who have not had disease progression or are non-evaluable at the interim or final analyses will be censored on the date they were last evaluated. For OS, patients will be followed until either lost to follow-up, withdrawal, or death. Patients will be censored on the date they were last known to be alive, regardless of disease status: patients who discontinue post-randomization but receive no study treatment will be censored on the date of their last known vital status.

For AEs, missing dates will not be imputed; however if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

14.4. Changes in the Conduct of the Study or Planned Analysis

Following an annual review of clinical safety data (29 July 2015), a dose reduction is being implemented. Under Protocol Versions < 5.0, the selinexor group was prescribed a dose equivalent to ~55 mg/m^2 twice weekly based on the patient's BSA. Under Protocol Versions ≥ 5.0, the selinexor group will receive a fixed dose of 60 mg (equivalent to ~35 mg/m^2) twice weekly. As described above, patients enrolled under Protocol Versions < 5.0 will not be included in the efficacy analysis, but will be included in the safety analyses.

All deviations from the original statistical analysis plan will be documented and provided in the final clinical study report.

15. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

15.1. Declaration of Helsinki

The Study will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki.

15.2. Good Clinical Practice

This study will be conducted according to the approved study protocol and Standard Operating Procedures (SOPs) that meet the guidelines provided by the International Conference on Harmonisation (ICH) E6 for Good Clinical Practice in clinical studies.

15.3. Institutional Review Boards/Ethics Committees

Before implementing this study, the protocol, the proposed patient informed consent forms and other information for the patients, must be reviewed by a properly constituted committee or committees responsible for approving clinical studies. The IRB/IEC written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title, date and version number), and of the patient informed consent form (date, version).

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, the IRB/IEC and the Health Authorities.

15.4. Regulatory Authority Approval

Before implementing this study, the protocol must be approved by the relevant regulatory authority.

15.5. Pre-study Documentation Requirements

To be provided.

15.6. Informed Consent

The investigator must fully inform the patient of all pertinent aspects of the trial including the written information approved/favorably assessed by the IRB/IEC.

Prior to the start of the pre-study examination, the written informed consent form must be signed and personally dated by the patient and by the physician who conducted the informed consent discussion. One copy of the written information and signed consent form must be given to each patient and 1 copy must be retained in the investigator's study records.

Additionally, consent will be requested to obtain/retain a blood sample for future analysis as warranted by our rapidly-advancing understanding in this field. Each patient’s Informed Consent document will reflect that samples collected may be used for pharmacogenomic investigations.

15.7. Patient Confidentiality and Disclosure

Data on patients collected on eCRFs during the trial will be documented in an anonymous fashion and the patient will only be identified by the patient number, and by his/her initials if

also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial patients. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a patient participating in the trial is violated. Likewise, the appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

15.8. Collection, Monitoring and Auditing Study Documentation, and Data Storage

15.8.1. Collection of Data and Monitoring Procedures

This study will use a 21 CFR Part 11 compliant electronic data capture system (TEMPO™) An electronic case report form (eCRF) is used for data recording All data requested on the eCRF must be entered and all missing data must be accounted for. Any observations must be reported to the sponsor.

The data will be checked for completeness and correctness as it is entered by the real-time online checks applied by TEMPO™. Off-line checks will also be run to perform any additional data review required. Discrepancy reports will be generated accordingly and transferred to the study center for resolution by the investigator or his/her designee.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRF against the investigator's records by the study monitor (source document verification), and the maintenance of a study drug–dispensing log by the investigator.

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor representative will review the protocol and case report forms with the investigators and their staff. During the study a monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the case report forms, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment. The monitor will ensure during on-site visits that study medication is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the monitors during these visits. All critical observation or compliance issues will be reported to sponsor Head of Quality and Regulatory Affairs.

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the case report form entries. No information in these records about the identity of the patients will leave the study center. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

15.8.2. Auditing Procedure

In addition to the routine monitoring procedures the Sponsor or the regulatory authority can conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of Good Clinical Practice (GCP).

The investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

In the event that a major compliance or regulatory issues arises, the sponsor may conduct an audit without prior schedule.

15.8.3. Retention of Documents

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc., and keep a copy of the signed informed consent form. All information on case report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the case report forms, which will be documented as being the source data.

15.9. Disclosure of Information

All information provided to the investigator by Karyopharm, or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than to Karyopharm, or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

15.10. Discontinuation of the Study

It is agreed that, for reasonable cause, either the investigator or Karyopharm, may terminate the investigator’s participation in this study after submission of a written notice. Karyopharm may terminate the study at any time upon immediate notice for any reason, including the Sponsor’s belief that discontinuation of the study is necessary for the safety of patients.

15.11. Study Report, Publication Policy and Archiving of Study Documentation

15.11.1. Study Report and Publication Policy

An ICH-compliant integrated clinical and statistical report will be prepared upon completion of the study and data analysis. The results of the study will be published in a relevant peer-reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor.

15.11.2. Data Capture

The eDC vendor will be responsible for the design of the eCRF, monitoring the trial according to GCP guidelines, preparation of data queries and reports to assist the clinical monitoring, and training each study site staff member entering data in the eCRF. The eDC vendor will also be responsible for preparation of analysis files from the database prior to analyses, assisting with the statistical analyses and statistical report, and preparation of the integrated clinical study report.

The eDC component of TEMPO™ will be used for electronic data acquisition and storage. TEMPO™ will provide electronic case report forms (eCRFs) for transfer of all research data by site personnel from data source documentation to the study database. Each responsible person at a site will have user access to TEMPO™ through their unique username and password, with permissions providing each person their needed access. Some personnel will have data entry, data review, and query resolution permissions, while others may only have data read permissions, based on their individual study roles. TEMPO™ is flexible to allow customizable permissions as needed for study personnel.

Study data will be checked for completeness and correctness as it is entered by the real-time online checks applied by TEMPO™. Off-line checks will also be run to perform any additional data review required. Any issues identified will be transferred to the study site via query for resolution by the investigator or his/her designee. All queries will be managed through TEMPO™ and audit trails of all queries and their resolution, along with any data changes, will be recorded.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Clinical research associates (CRAs) will monitor the data, verifying all captured data against its source. Monitoring will be enhanced by computer assisted data management identifying missing or possibly erroneous data as soon as data is entered into the system. This approach will allow initial remote monitoring, and communication between CRAs and site personnel before and between site visits, and will expedite data review and cleaning. Missing data and identified data errors (or possible errors) will be communicated by the CRAs to site investigators using the Query feature in TEMPO™ for correction or acknowledgement that data is correct as entered. As each subject's data entry is completed and fully monitored with all queries resolved, that subject's data will be locked by the CRA to only allow read access for the remainder of the study.

TEMPO™ and all study data are housed in a secure computing environment. TEMPO™ further provides a complete audit trail of all data entry, monitoring, and query activity. TEMPO™ is compliant with HIPPA and meets all requirements for 21 CFR Part 11.

15.11.3. Study Documents

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc.,

and keep a copy of the signed informed consent form. All information on the e-case report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the e-case report forms, which will be documented as being the source data.

15.11.4. Archiving of Documents

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations. The Sponsor will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include, but are not limited to:

1. IRB/IEC/REB approvals for the study protocol and all amendments
2. All source documents and laboratory records
3. CRF copies (electronic copies on a CDROM)
4. Patients' informed consent forms (with study number and title of trial)
5. FDA form 1572
6. Any other pertinent study document

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17. APPENDICES

APPENDIX 1 Disease Risk Assessment According to the European LeukemiaNet (ELN)

Table 1. Standardized Reporting for Correlation of Cytogenetic and Molecular Genetic Data in Acute Myeloid Leukemia With Clinical Data According to the ELN Guideline

ELN Genetic Risk Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3-ITD* (normal karyotype) Mutated *CEBPα* (normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3-ITD* (normal karyotype) Wild-type *NPM1* and *FLT3-ITD* (normal karyotype) Wild-type *NPM1* without *FLT3-ITD* (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged −5 or del(5q); −7; abnl(17p); complex karyotype

Abbreviation: ELN, European LeukemiaNet.

Table from:

Röllig C, Bornhäuser M, Thiede C, Taube F, Kramer M, Mohr B, Aulitzky W, Bodenstein H, Tischler HJ, Stuhlmann R, Schuler U, Stölzel F, von Bonin M, Wandt H, Schäfer-Eckart K, Schaich M, Ehninger G. Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the EuropeanLeukemiaNet recommendations: evaluation of the proposed reporting system. *J Clin Oncol*. 2011 Jul 10;29(20):2758-65.

APPENDIX 2 International Working Group Guidelines for AML

Response Criteria for AML (modified from Cheson et al. 2003)

Reference: Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Este EH, et al. 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. *J Clin Oncol.* 2003 Dec;21(24):4642-4649.

Acute Myeloid Leukemia (AML) is a clonal expansion of myeloid blasts in bone marrow, blood, or other tissue (ICD-O code 961/3. The most significant change from the FAB classification is that the requisite blast percentage for a diagnosis of AML be ≥ 20% myeloblasts in the blood or marrow.

There are two exceptions to the above rule.

- Acute erythroleukemia (erythroid/myeloid subtype) is defined by the presence in the bone marrow of greater than or equal to 50% erythroid precursors in the entire nucleated cell population and greater than or equal to 20% myeloblasts in the non-erythroid cell population.

- Pure erythroid leukemia is defined as a neoplastic proliferation of immature cells committed exclusively to the erythroid lineage (> 80% of the marrow nucleated cells) with no evidence of a significant myeloblastic component.

Diagnostic and Staging Criteria

Definitions:

1. Bone marrow cellularity: The volume of hematopoietic nucleated cells, expressed as a percentage of marrow volume less volume of fibrosis.
2. Blasts: For AML, the following cell types are considered equivalent to blasts and are included in the calculation of blast percentages. (Note that erythroblasts are not counted as blasts in calculating blast percentages).
    a. Myeloblasts include both agranular and granular variants.
    b. Neoplastic promyelocytes, for Acute Promyelocytic Leukemia. Neoplastic promyelocytes are defined as promyelocytes with heavy granulation and irregular nuclei and/or primitive promyelocytes with very large numerous Auer rods.
    c. Monoblasts and promonocytes for Acute Monoblastic and Monocytic Leukemia
    d. Megakaryoblasts for Acute Megakaryoblastic Leukemia.
3. Bone Marrow Blast Percentage is calculated as the percent of blasts among all nucleated marrow cells.

Table A4.1: Response Criteria in AML

Response Criterion	Neutrophils (µL)	Platelets (µL)	Bone Marrow Blasts (%)	Other
Early treatment assessment	NA	NA	< 5	
Morphologic leukemia—free state	NA	NA	< 5	Flow cytometry EMD
Morphologic CR	> 1,000	> 100,000	< 5	Transfusion EMD
Cytogenetic CR	> 1,000	> 100,000	< 5	Cytogenetics – normal EMD
Molecular CR	>1,000	> 100,000	< 5	Molecular-negative EMD
Partial remission (PR)	>1,000	> 100,000	≥ 50% decrease to 5-25% OR Blasts < 5% if Auer rod positive	

Abbreviations: AML, acute myelogenous leukemia; EMD, extramedullary disease; CR, complete remission.

Descriptive Definitions of Remission

A. **Morphologic complete remission (CR):** ANC ≥ 1,000/ µL, platelet count ≥ 100,000/µL, < 5% bone marrow blasts, no Auer rods, no evidence of extramedullary disease. (No requirements for marrow cellularity, hemoglobin concentration).

B. **Morphologic complete remission with incomplete blood count recovery (CRi):** Same as CR but ANC may be < 1,000/ µL and/or platelet count < 100,000/ µL.

C. **Partial remission (PR):** ANC > 1,000/ µL, platelet count > 100,000/ µL, and at least a 50% decrease in the percentage of marrow aspirate blasts to 5-25%, or marrow blasts < 5% with persistent Auer rods.

D. **Morphologic leukemia-free state (MLFS):** This designation requires less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There should be no blasts with Auer rods or persistence of extramedullary disease. The presence of a unique phenotype (by flow cytometry) identical to what was found in the pretreatment specimen (e.g., CD34, CD7 coexpression) should be viewed as persistence of leukemia.

E. **Stable Disease (SD):** Not fulfilling criteria for CR, CRi, PR, MLFS, or disease progression

F. **Disease Progression (PD):** Presence of > 50% increase in bone marrow blasts to a level of at least 50% and/or a doubling of the percentage of peripheral blood blasts to a level of at least 50%.

G. **Inevaluable (IN):** This box should be checked off if no hematologic evaluation done or if a bone marrow aspirate and/or biopsy was done and there were no spicules/fragments in the aspirate (and biopsy was not representative, if done).

APPENDIX 3 Ophthalmic Examination: Assessments and Grade 1-4 Grading System for Cataracts

An ophthalmic examination by an optometrist or ophthalmologist is required at screening, if clinically indicated during the study (e.g., monitoring of pre-existing cataracts, visual disturbances) and at the Final Visit.

The examination is to include the following:

Prior to dilation:

- best corrected visual acuity
- slit lamp examination
- tonometry

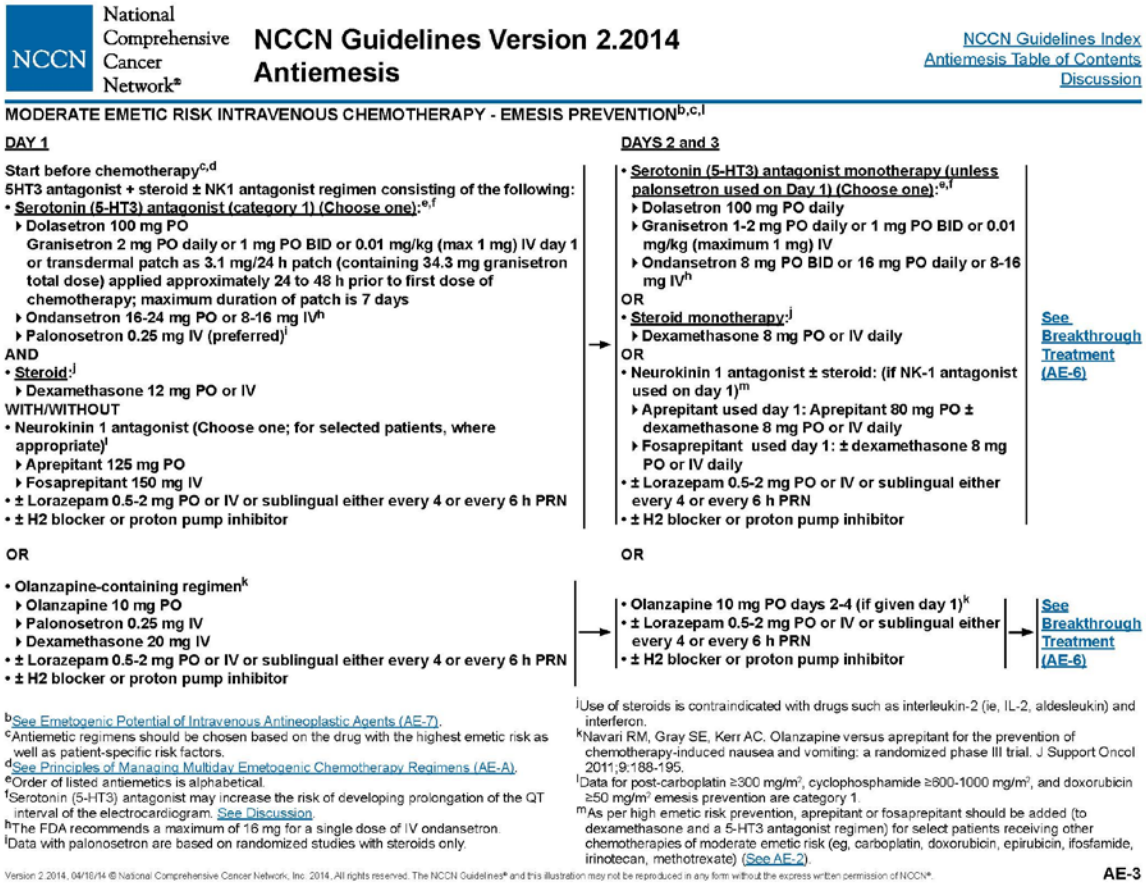
Following dilation:

- fundoscopy
- 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 (modified from Optometric Clinical Practice Guideline: Care of the Adult Patient with Cataracts: available on the American Optometric Association website: www.aoa.org). However, patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the Grade 1-4 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 opacity	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.				

APPENDIX 4 NCCN Clinical Practice Guidelines in Oncology: Antiemesis



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Antiemesis

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Discussion

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

OR

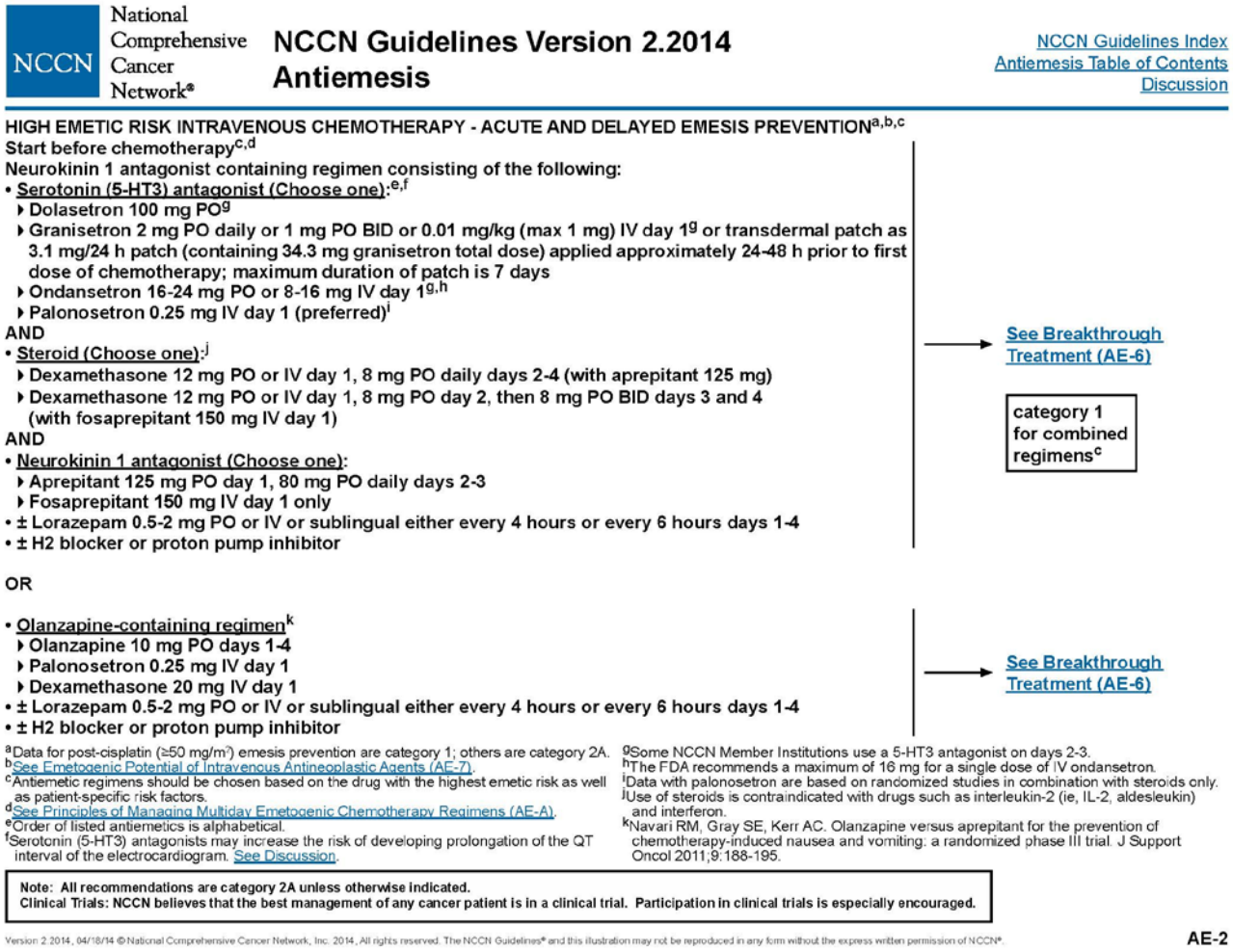
- Olanzapine 10 mg PO days 2-4 (if given day 1)[k]
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor

See Breakthrough Treatment (AE-6)

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/m², cyclophosphamide ≥800-1000 mg/m², and doxorubicin ≥50 mg/m² 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



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Antiemesis

NCCN Guidelines Index
Antiemesis Table of Contents
Discussion

HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION[a,b,c]
Start before chemotherapy[c,d]
Neurokinin 1 antagonist containing regimen consisting of the following:
- **Serotonin (5-HT3) antagonist (Choose one):[e,f]**
  - Dolasetron 100 mg PO[g]
  - Granisetron 2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1[g] or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24-48 h prior to first dose of chemotherapy; maximum duration of patch is 7 days
  - Ondansetron 16-24 mg PO or 8-16 mg IV day 1[g,h]
  - Palonosetron 0.25 mg IV day 1 (preferred)[i]

AND
- **Steroid (Choose one):[j]**
  - Dexamethasone 12 mg PO or IV day 1, 8 mg PO daily days 2-4 (with aprepitant 125 mg)
  - Dexamethasone 12 mg PO or IV day 1, 8 mg PO day 2, then 8 mg PO BID days 3 and 4 (with fosaprepitant 150 mg IV day 1)

AND
- **Neurokinin 1 antagonist (Choose one):**
  - Aprepitant 125 mg PO day 1, 80 mg PO daily days 2-3
  - Fosaprepitant 150 mg IV day 1 only
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4**
- **± H2 blocker or proton pump inhibitor**

→ See Breakthrough Treatment (AE-6)

category 1 for combined regimens[c]

OR

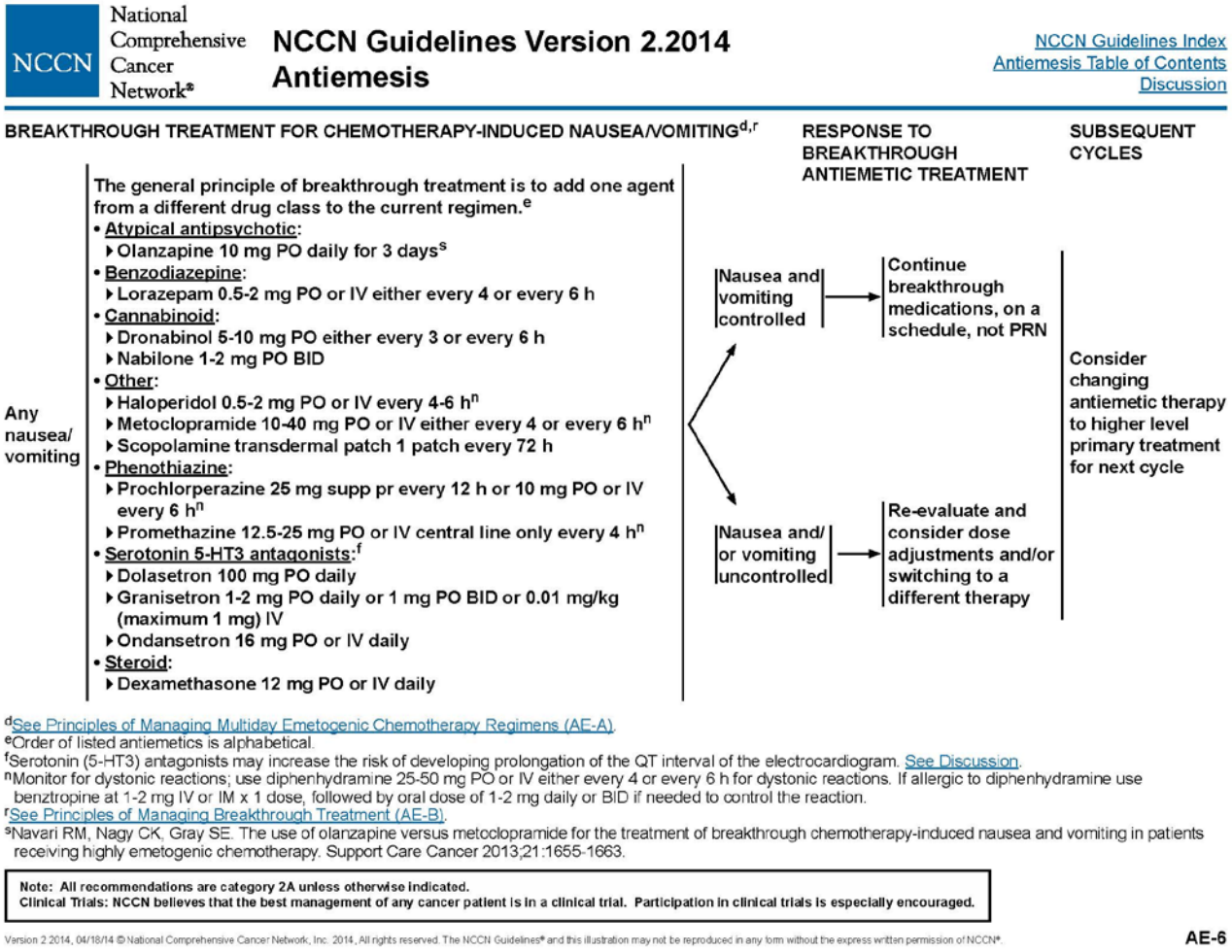
- **Olanzapine-containing regimen[k]**
  - Olanzapine 10 mg PO days 1-4
  - Palonosetron 0.25 mg IV day 1
  - Dexamethasone 20 mg IV day 1
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4**
- **± H2 blocker or proton pump inhibitor**

→ See Breakthrough Treatment (AE-6)

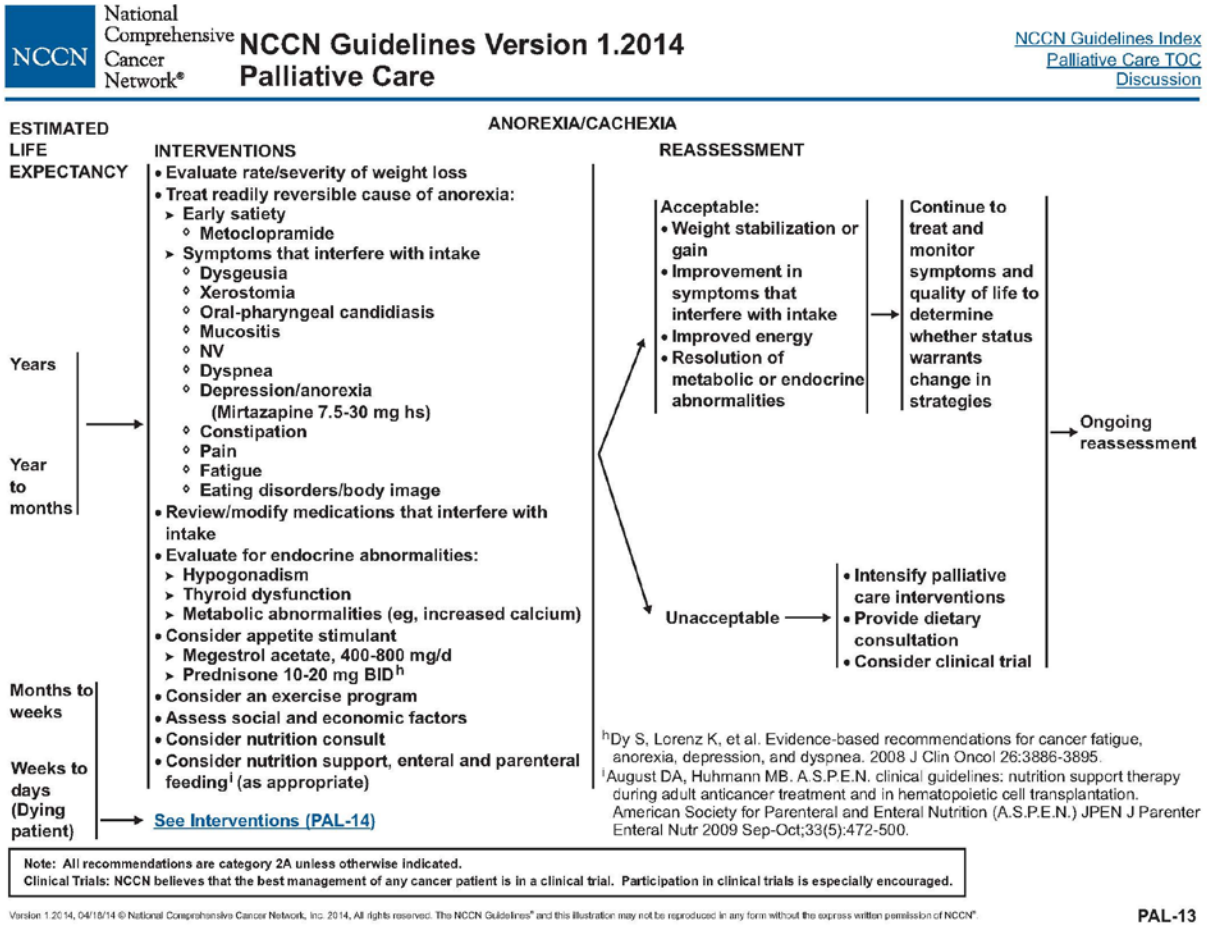
[a] Data for post-cisplatin (≥50 mg/m²) emesis prevention are category 1; others are category 2A.
[b] See Emetogenic Potential of Intravenous Antineoplastic Agents (AE-7).
[c] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors.
[d] See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
[e] Order of listed antiemetics is alphabetical.
[f] Serotonin (5-HT3) antagonists may increase the risk of developing prolongation of the QT interval of the electrocardiogram. See Discussion.
[g] Some NCCN Member Institutions use a 5-HT3 antagonist on days 2-3.
[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 in combination 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

AE-2



APPENDIX 5 NCCN Clinical Practice Guidelines in Oncology: Anorexia/Cachexia



APPENDIX 6 Glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products (representative List)

Glutathione (GSH)		N-acetylcysteine (NAC)		S-adenosylmethionine (SAM)	
Product Name	**Ingredient**	**Product Name**	**Ingredient**	**Product Name**	**Ingredient**
Glutathione	glutathione	Antidote for acetaminophen overdose	acetylcysteine	SAM-e Complete	S-adenosyl-methionine
L-Glutathione	L-glutathione	Cerefolin NAC: medical food for age-related memory loss	L-methylfolate vitamin B12 N-acetyl cysteine	SAMe	S-adenosyl-L-methionine
Glutathione reduced	glutathione	NAC	N-acetyl cysteine	Double Strength SAMe 400	S-adenosyl-methionine
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	N-A-C Sustain	N-acetyl L-cysteine		
Glutathione, Cysteine & C	glutathione L-cysteine vitamin C	Best NAC Detox Regulators	N-acetyl cysteine		
(Mega-) Liposomal Glutathione	glutathione				
Lypospheric GSH	glutathione				
Ivory Caps Skin Enhancement Formula	glutathione				

APPENDIX 7 Protocol amendments: Rationales and Summaries of changes

CLINICAL STUDY PROTOCOL

KCP-330-008

A RANDOMIZED, OPEN LABEL, PHASE 2 STUDY OF THE SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE) SELINEXOR (KPT-330) VERSUS SPECIFIED PHYSICIAN'S CHOICE IN PATIENTS ≥ 60 YEARS OLD WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA (AML) WHO ARE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY AND/OR TRANSPLANTATION

SOPRA Study: Selinexor (KPT-330) in Older Patients with Relapsed AML

Drug Development Phase:	Phase 2
Investigational Product:	Selinexor (KPT-330)
Indication:	Acute Myeloid Leukemia
EudraCT Number:	2014-000920-26
Sponsor:	Karyopharm Therapeutics, Inc. 85 Wells Avenue Newton, MA 02459 USA
Protocol Date and Version:	21 January 2014, Version 1.0 03 July 2014, Version 2.0 (Amendment 1) 30 September 2014, Version 2.1 (United Kingdom-specific Amendment 2) 25 November 2014, Version 3.0 (Amendment 3) 24 April 2015, Version 4.0 (Amendment 4) 09 July 2015, Version 4.1 (Germany-specific Amendment 4.1) 04 August 2015, Version 5.0 (Amendment 5)

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

Amendment 5.0, Version 5.0

Version 5.0 incorporates changes to Version 4.0, as well as Germany-specific changes in Version 4.1

- *Please note that Germany-specific Version 4.1 included Version 3.0 to 4.0 changes; these changes were marked in the text of the Version 4.0 redline and are not repeated in the Version 5.0 redline*

Amendment Rationale

The major changes in this amendment of the protocol were made primarily to address an unexpected increase in the number of infection-related AEs in patients randomized to selinexor as compared with patients randomized to the Physician's Choice arm. Minor updates to other safety assessment and guidance sections are also included. Specific major changes are as follows:

- Reduction of selinexor dose from ~55 mg/m^2 (~80-100 mg) to a fixed dose of 60 mg (~35 mg/m^2) to reduce selinexor-related adverse events, especially sepsis and pneumonia/lung infections in this highly compromised patient population.
- Revision of inclusion criteria to specify that prior AML therapy must have included an adequate trial of a hypomethylating agent with at least 2 cycles.
- Addition of exclusion for patients who are classified as favorable according to the European LeukemiaNet (ELN) disease risk assessment.
- Revision of statistical methods, including ITT and PP populations and presentation of non-efficacy data, to reflect exclusion of patients treated with ~55 mg/m^2 of selinexor from the primary analysis population due to changes in the selinexor dose and the inclusion criteria. These patients will be included in the safety population. As such, the total number of patients in the study has been increased.
- Changes to guidance on the use of hydroxyurea requested by German (Ulm EC) that were included in Version 4.1.

Other changes, primarily editorial and administrative, were made for readability and clarity. These changes include updates to data and corrections in the Synopsis, Schedule of Assessments, body of the protocol and Appendices for consistency and accuracy.

The revised protocol Version 5.0 dated 04 August 2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of the key changes that were made to Version 4.0 of the protocol, including the rationale for these changes, in Version 5.0 is provided below.

Changes to the protocol

Administrative Changes

- Internal changes to improve clarity and eliminate inconsistencies between sections; updated Table of Contents and hyperlinks (**Modified sections**: Global).
- Updated the version number and date of protocol Version 4.0 dated 24 April 2015 to Version 5.0 dated 04 August 2015 (**Modified sections**: Global).
- Updated abbreviations list, references, patient numbers and safety/response data (**Modified sections**: Global).
- Removed sample FACT-Leu QOL and EQ-5D-5L questionnaires from Appendices. The questionnaires will be located in the Investigator Site File.

Clinical Experience

- Addition of new subsection on risk of sepsis in AML with a summary of the clinical safety data reviewed in July 2015 (29 July 2015) that indicate an apparent increase in the rates of sepsis at higher doses of selinexor.
    - **Modified Section:** 4.3.1.
    - **Rationale:** To reflect recent safety findings in this study regarding increased rate of sepsis and possibly pneumonia/lung infections in patients treated with selinexor.

Study Design

- Addition of daily temperature diary to be completed by all patients.
    - **Modified Sections:** Sections 9.2.3, 9.2.4, 9.2.5, 9.2.6, 9.2.7, and 9.2.8, and Table 1.
    - **Rationale:** To increase safety oversight of this highly compromised population in response to recent sepsis findings.
- Addition of visit on Cycle 1 Day 4, weekly phone calls for all patients during all subsequent weeks in Cycles 1-3, and weekly visits on Days 8 and 22 of Cycle 2.
    - **Modified Sections:** Sections 9.2.4, 9.2.5, 9.2.6, and 9.2.7, and Table 1.
    - **Rationale:** To increase safety oversight of this highly compromised population in response to recent sepsis findings.
- Removed the anticipated enrollment period of 15-18 months.
    - **Modified Sections:** Synopsis (Study Duration and Statistical Methods) and Section 14.1.2.
    - **Rationale:** This enrollment estimate is not informative to the investigators.
- Addition of a review of safety data for all patients at each interim analysis.
    - **Modified Sections:** Sections 7.2 and 14.2.1.4.
    - **Rationale:** To allow for review of all patient safety data by the DSMB in conjunction with the interim analyses on the ITT population.
- Revised the timing of completion of follow-up was also revised from 6 months after randomization to 6 months after the end of treatment.
    - **Modified Sections:** Synopsis (Study Duration and Statistical Methods), Section 7.1, Section 11.2, Section 11.3, Section 14.1.2

  - **Rationale:** To more completely assess safety and survival for all patients.
- Clarified the guidance on missed doses
  - **Modified Sections:** Section 12.3.1.6.1.
- Modified patient numbers: total number of patients increased to 300 and the number of patients in the primary analysis was corrected from 170 patients to 171 patients.
  - **Modified Sections:** Synopsis (Methodology), Section 8.1, Section 9.1, and Section 14.1.2.
  - **Rationale:** To reflect changes to dosing, inclusion and exclusion criteria, and study populations.
- Revised secondary objectives/endpoints to add morphologic leukaemia-free state (MLFS) and remove bone marrow CR from ORR
  - **Modified Sections:** Synopsis (Objectives), Section 6.2, Section 7.4.2, Section 10.1.4.
  - **Rationale:** To align nomenclature with response criteria for AML (IWG guidelines for AML).

Inclusion Criteria

- Revised inclusion criterion #6 to specify that prior AML therapy must have included an adequate trial of a hypomethylating agent with at least 2 cycles, and to clarify that patients must have progressed after their most recent therapy.
  - **Modified Sections:** Synopsis (Diagnosis and Main Criteria for Inclusion) and Sections 7.1, 8.3, and 9.
  - **Rationale:** To align the study population globally. The requirement for prior AML treatment with both cytosine arabinoside and an adequate trial of a hypomethylating agent will account for differences in treatment practices between the US and Europe.
- Revised inclusion criteria #8 to clarify that objective, documented evidence of disease progression is required for the most recent previous therapy prior to study entry.
  - **Modified Section:** Section 8.3.
  - **Rationale:** To align with the change to inclusion #6.
- Revised inclusion criterion #9 to allow patients with liver involvement of their AML who have an AST and ALT ≤ 5 x ULN to enroll in the study, to increase the threshold levels for inclusion for bilirubin (≤ 2 x ULN), AST (≤ 2.5 x ULN), and ALT (≤ 2.5 x ULN), and to specify the threshold level (≤ 3 x ULN) for patients with high indirect bilirubin due to a congenital disorder (Gilbert's syndrome).
  - **Modified Section:** Section 8.3.
  - **Rationale:** To enable patients with hepatic transaminase elevations due to liver involvement of their AML to enroll in the study and to align inclusion requirements for bilirubin, AST, and ALT with other Karyopharm clinical studies in hematological cancers. In addition, of note, liver function abnormalities are rarely associated with selinexor use.

Exclusion Criteria

- Added an exclusion for patients whose AML is classified as favorable according to the European LeukemiaNet (ELN) disease risk assessment.
    - **Modified Sections:** Synopsis (Major Exclusion Criteria) and Section 8.4.
    - **Rationale:** To further define the appropriate patient population. Patients whose AML is classified as intermediate or adverse according to ELN are in greater need of treatment than patients whose AML is classified as favorable, who have a more benign course of disease.

Treatment

- Changed starting selinexor dose from ~55 mg/m^2 (~80-100 mg) to 60 mg (~35 mg/m^2) fixed dose for all patients.
    - **Modified Sections**: Synopsis (Test Product, Dose and Mode of Administration) and Sections 4.3, 5.1, 7.1, 8.1, 9.1, 12.2.3, 12.3.1 (Table 5), 14.1.2, and 14.4.
    - **Rationale:** Reduction of selinexor dose from ~55 mg/m^2 (~80-100 mg) to a fixed dose of 60 mg (~35 mg/m^2) to reduce selinexor-related adverse events, especially sepsis and pneumonia/lung infections in this highly compromised patient population.
- Deletion of hydroxycarbamide (hydroxyurea) guidance text from Test Product, Dose and Mode of Administration (synopsis) and Prohibited Medication Section 12.3.4)
    - **Modified Sections**: Synopsis (Test Product, Dose and Mode of Administration) and Section 12.3.4 (Prohibited Medication).
    - **Rationale:** Text removed to improve protocol consistency and clarity, as text is not appropriate for these sections (i.e., it does not belong in the named sections). Guidance regarding the use of hydroxycarbamide (hydroxyurea), including contraindications, is provided in Supportive Care and Concomitant Medications section of the synopsis and protocol Sections 7.1 and 12.3.3.1.

Supportive Care and Concomitant Medications

- Modification of text regarding the use of hydroxycarbamide (hydroxyurea), including additional guidance regarding contraindications (changes requested by German (Ulm) EC)
    - *Original Text:*
        - "Patients receiving selinexor will also receive BSC including blood product transfusions, antimicrobials, and (if appropriate) granulocyte colony-stimulating factors for neutropenic infection. Hydroxyurea may be used at any time during the study but only in patients with WBC ≥ 30,000/μL." [Section 7.1]

      AND
        - "Hydroxyurea may be used at any time during the study but only in patients with WBC ≥ 30,000/μL." [Synopsis, Section 12.3.4]
    - *Amended Text*: "Hydroxyurea may be used at any time during the study, typically in patients with WBC ≥30,000/μL or per institutional guidelines. Prior to the initiation of hydroxyurea please consider the contraindications in the

Summary of Product Characteristic (SPC), including leukocytopenia (< 2.5 x 10^9 leukocytes/L), thrombocytopenia (< 100 x 10^9 platelets/L) or severe anemia."

- **Modified Sections**: Synopsis (Supportive Care and Concomitant Medications) and Sections 7.1, 12.3.3.1, and 12.3.4.
- **Rationale:** This change was made to address the two requests from the Ulm EC for modification of the guidance regarding the use of hydroxycarbamide (hydroxyurea), including contraindications. The specific wording requested by the ULM EC has been modified slightly for clarity. The requests for protocol changes, which, are summarized below:
  - Addition of text regarding thrombocytopenia and severe anemia as contraindications for the use of hydroxycarbamide (hydroxyurea)
  - Modification of the following text in Study Design, page 43, paragraph 6 (version 3.0 redline):

    "Patients receiving selinexor will also receive BSC including blood product transfusions, antimicrobials, and (if appropriate) granulocyte colony-stimulating factors for neutropenic infection and hydroxyurea (Cycle 1 only)" **is to be deleted and replaced by**: "Hydroxyurea may be used at any time during the study but only in patients with WBC ≥ 30,000 μl".

- Modification of guidance for anorexia and neutropenia to strongly encourage the use of megesterol for patients with anorexia and prophylactic antimicrobials for patients with neutropenia.
  - **Modified Sections**: Table 6 and Section 12.3.2.3.
  - **Rationale:** This change was made for patient safety to mitigate complications related to anorexia and neutropenia.
- Modification of guidance in "Dose Adjustments with Changes in BSA"
  - **Modified Sections**: Section 12.3.1.5.
  - **Rationale:** This change was made to reflect the switch to the fixed 60 mg dose.

Adverse Events

- Modified pregnancy text to replace text relating to a drug-drug interaction (i.e., pregnancy due to study drug reduction of the effectiveness of a contraceptive medication) with text relating to adverse events (i.e., medical occurrence observed in the mother or fetus/newborn).
  - **Modified Section:** 13.1.4.
  - **Rationale:** Change was made to improve accuracy.

Statistical Methods

- Revised stratification: replaced age < 70 versus age ≥ 70 years with number of prior therapies, 1 versus >1, added a stratum for peripheral leukemic blast counts

≥ 10,000/μL versus < 10,000/μL, and reduced the duration of the first CR on prior therapy from 1 year to 6 months.
    - **Modified Sections:** Synopsis (Methodology, Diagnosis and Main Criteria for Inclusion) and Sections 7.1, 7.5, 9.1, 14.1.2, and 14.1.4.
    - **Rationale:** The stratum for age was replaced by stratum for number of prior therapies as number of prior therapies is a more relevant factor affecting potentially correlating with clinical outcome, given the change in inclusion criteria relating to number of prior therapies. The stratum for peripheral leukemic blast counts has been added to explore correlation between WBC count and clinical outcome. The duration of the first CR on prior therapy stratum has been reduced to reflect a more relevant cut off for older patients with relapsed AML for whom median OS is 7-9 months.
- Revised statistical methods to increase the patient population, redefine the ITT and PP populations to exclude patients enrolled under Protocol Versions < 5.0, clarify the presentation of non-efficacy data, and revise the populations to be included in the interim analyses.
    - **Modified Sections:** Synopsis (Methodology; Reference Therapy Dose and Mode of Administration; Statistical Methods) and Sections 7.2, 8.1, 9.1, 14.1.2, 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.3, 14.3.3, 14.3.6, and 14.4.
    - **Rationale:** To reflect the exclusion of patients treated with ~55 mg/m^2 of selinexor from the primary analysis population due to changes in the selinexor dose and the inclusion criteria.
- Revised secondary objectives/endpoints to add mCRR and remove bone marrow CR from CRR.
    - **Modified Sections:** Synopsis (Objectives, Criteria for Evaluation) and Sections 6.2, 7.4.2, 10.14, and 14.3.4.
    - **Rationale:** To align with updates to the SAP.
- Added details on sample size re-assessment for the second interim analysis.
    - **Modified Sections:** Sections 14.1.2 and 14.2.1.4.
    - **Rationale:** FDA request.

Protocol Version 4.1 (Amendment 4.1)

Amendment Rationale

The major changes in this amendment of the protocol are as follows:

- Address comments, dated 06.05.2015, from the Ethics Committee of Ulm (Ulm University) including requests for additional revisions to KCP-330-008 Version 3.0 (Ulm reference number 122/14) to provide additional guidance regarding the use of hydroxycarbamide (hydroxyurea). Version 4.1 is for Germany only; these changes will be carried forward into a future global version of the protocol.
- Increase in the assumed drop out rate to ~20% to align with the actual rate at study sites and increase in the sample size to 170 patients to maintain power with the increased drop out rate.
- Addition of interim analysis after 25% of Overall Survival events in order to assess for early futility and prevent unnecessary exposure of patients to selinexor in the event futility is declared.
- Expansion of exclusion criteria to exclude patients with concurrent active malignancies that are not being treated.
- Addition of EQ-5D-5L Quality of Life questionnaire.
- Addition of 20 mg tablets in blister packs as an option for selinexor drug product.
- Removal of specific recommendation for the use of dexamethasone as a supportive care agent.

Other changes, primarily editorial and administrative, were made for readability and clarity. These changes include updates to data and corrections in the Synopsis, Schedule of Assessments, and body of the protocol for consistency and accuracy.

Version 4.1 is for Germany only. The revised protocol Version 4.1 dated 09 July 2015 will be submitted by the Principal Investigator(s) to all applicable German Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of the key changes that were made to Version 4.1 of the protocol, including the rationale for these changes, in Version 3.0 is provided below.

Changes to the protocol

Administrative Changes

- Internal changes to improve clarity and eliminate inconsistencies between sections; updated Table of Contents and hyperlinks (**Modified sections**: Global).
- Updated the version number and date of protocol from Version 3.0 dated 24 November 2014 to Version 4.1 dated 09 July 2015 (**Modified sections**: Global).
- Updated references and patient and incidence data (Modified sections: Global).
- Removed sample FACT-leu QOL questionnaire from Appendix 2. The questionnaire will be located in the Investigator Site File.

Concurrent Therapies (Supportive Care and Concomitant Medications)

- Modification of text regarding the use of hydroxycarbamide (hydroxyurea), including additional guidance regarding contraindications.

Original Text:

"Patients receiving selinexor will also receive BSC including blood product transfusions, antimicrobials, and (if appropriate) granulocyte colony-stimulating factors for neutropenic infection. Hydroxyurea may be used at any time during the study but only in patients with WBC ≥ 30,000/μL." [Section 7.1]

AND

"Hydroxyurea may be used at any time during the study but only in patients with WBC ≥ 30,000/μL." [Synopsis, Section 12.3.4]

Amended Text:

"Hydroxyurea may be used at any time during the study but only in patients with WBC ≥ 30,000/μL. Prior to the initiation of hydroxyurea please consider the contraindications in the Summary of Product Characteristic (SPC), including leukocytopenia (< 2.5 x 10^9 leukocytes/L), thrombocytopenia (< 100 x 10^9 platelets/L) or severe anemia."

- **Modified Sections**: Synopsis (Supportive Care and Concomitant Medications), Sections 7.1, 12.3.3.1, and 12.3.4.
- **Rationale:** This change was made to address the two requests from the Ulm EC for modification of the guidance regarding the use of hydroxycarbamide (hydroxyurea), including contraindications. The requests for protocol changes are summarized below:

  - Addition of text regarding thrombocytopenia and severe anemia as contraindications for the use of hydroxycarbamide (hydroxyurea)
  - Modification of the following text in Study Design, page 43, paragraph 6 (Version 3.0 redline):

    "Patients receiving selinexor will also receive BSC including blood product transfusions, antimicrobials, and (if appropriate) granulocyte colony-stimulating factors for neutropenic infection and hydroxyurea (Cycle 1 only)" **is to be deleted and replaced by**: "Hydroxyurea may be used at any time during the study but only in patients with WBC ≥ 30,000 μL".

Test Product, Dose and Mode of Administration & Prohibited Medications Sections

- Deletion of hydroxycarbamide (hydroxyurea) guidance text from the Test Product, Dose and Mode of Administration subsection of the Synopsis and the Prohibited Medication subsection (Section 12.3.4).
    - **Modified Sections**: Synopsis (Test Product, Dose and Mode of Administration), Section 12.3.4 (Prohibited Medication).
    - **Rationale:** Text was removed to improve protocol consistency and clarity, as text is not appropriate for these sections (i.e., it does not belong in the named sections). Guidance regarding the use of hydroxycarbamide (hydroxyurea), including contraindications, is provided in Supportive Care and Concomitant Medications subsection of the synopsis and Sections 7.1 and 12.3.3.1 of the protocol.

Clinical Experience

- ***AML efficacy and safety data:*** Section describing efficacy and safety data from AML patients treated with selinexor in Phase 1 study KCP-330-001 was updated based on the presentation made at the EHA Annual Meeting 12-15 June 2014 (Garzon R, Flinn I, Berdeja J, et al.) and on information in the Selinexor/KPT-330 IB v 4.0 (April, 2015).
    - **Modified Sections:** Table 4-1 and Sections 4.3 and 5.
    - **Rationale:** To present currently available efficacy and safety data from AML patients treated with selinexor.
- ***Potential Risks:*** Side effects were updated based on information in the Selinexor/KPT-330 IB v 4.0 (April, 2015).
    - **Modified Section:** Section 4.3.1.
    - **Rationale:** To present currently available safety data for patients treated with selinexor.
- ***Reproductive Risks:*** Modified section to include summary of animal reproductive toxicity findings and statement that, as human reproductive risks are not known, all patients must use effective contraception as defined in Section 12.3.3.1 – Prevention of Pregnancy.
    - **Modified Section:** Section 4.3.1.1 (new section heading).
    - **Rationale:** Former language in this section only dealt with risk mitigation (contraception) without describing existing reproductive toxicity data.

Rationale for Dosing

- Addition of maximum allowable dose.
    - **Modified Sections:** Sections 5.1 and 12.3.1.5.
    - **Rationale:** To ensure no patient exceeds the maximum allowable dose.

Discontinuation Criteria

- Addition of End of Study section.
    - **Modified Sections:** Table 1-1, Section 11.3 (new sub-section).
    - **Rationale:** Provide definition of End of Study.

Study Design

- Increase in the assumed drop out rate from ~10% to ~20% and increase in the sample size from 150 patients to 170 patients.
  - **Modified Sections:** Synopsis, Sections 8.1, 9.1, and 14.1.2.
  - **Rationale:** Align with the actual drop out rate at the study sites and maintain power with the increased drop out rate.
- Addition of an interim analysis after 25% of Overall Survival events.
  - **Modified Sections:** Synopsis, Sections 7.2, 11.1, 14.1.2, and 14.2.1.4.
  - **Rationale:** Assess for early futility and prevent unnecessary exposure of patients to selinexor in the event futility is declared.
- Addition of BSA assessment at Days 1 and 15 of Cycles 2-5.
  - **Modified Sections:** Section 9.2.4 and Table 1-1.
  - **Rationale:** To ensure that none of the selinexor doses result in a dose > 70 mg/m^2.
- Increase in the anticipated enrollment period from 12 months to approximately 15-18 months.
  - **Modified Sections:** Synopsis and Section 14.1.2.
  - **Rationale:** Provide realistic timeframe for enrollment of additional patients.
- Clarification that patients who elect not to initiate study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained.
  - **Modified Sections:** Synopsis, Sections 7.1 and 11.2.
  - **Rationale:** Encourage patients who are randomized to physician's choice to provide follow-up information even if they choose not to initiate study treatment.
- Clarification of procedure for handling missing data for patients who are randomized but do not initiate study treatment.
  - **Modified Section:** Section 14.3.7.
  - **Rationale:** To account for missing data for randomized patients who do not receive study treatment.

Inclusion Criteria

- Revised inclusion criterion #9 to allow patients with liver involvement of their AML who have an AST and ALT ≤ 5 x ULN to enroll in the study, to increase the threshold levels for inclusion for bilirubin (≤ 2 x ULN), AST (≤ 2.5 x ULN), and ALT (≤ 2.5 x ULN), and to specify the threshold level (≤ 3 x ULN) for patients with high indirect bilirubin due to a congenital disorder (Gilbert's syndrome).
  - **Modified Section:** Section 8.3.
  - **Rationale:** Changes were made to enable patients with hepatic transaminase elevations due to liver involvement of their AML to enroll in the study and to align inclusion requirements for bilirubin, AST, and ALT with other Karyopharm clinical studies in hematological cancers. In addition, of note, liver function abnormalities are rarely associated with selinexor use.

Exclusion Criteria

- Expansion of exclusion criteria to exclude patients with concurrent active malignancies that are not being treated.
  - **Modified Section**: Section 8.4.
  - **Rationale:** To avoid compromising the objectives of the trial. Certain malignancies (e.g., CLL or prostate cancer), even if untreated, could compromise the trial objectives.

Treatment

- Addition of description of 20 mg selinexor tablet formulation, packaging and administration.
  - **Modified Sections**: Sections 12, 12.2.1, and 12.2.2.
  - **Rationale:** Change reflects pending addition of 20 mg selinexor tablets in blister packs as an additional form of selinexor drug product.
- Addition of new sub-section on Dose Modifications and Dose Delay (Section 12.3.1) to clarify criteria for dose modifications and discontinuation of patients due to dose delay.
  - **Modified Section:** Section 12.3.1 (new sub-section).
  - **Rationale:** Update of previous text to provide additional information and to improve clarity.
- Clarifications on restrictions on use of acetaminophen and GSH-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products.
  - **Modified Sections:** Section 12.3.4, Appendix 6.
  - **Rationale:** Minor revisions to improve clarity.
- Revision of Treatment Compliance (Section 12.5)
  - **Modified Section:** Section 12.5
  - **Rationale:** Update of previous text to provide additional information and to improve clarity.

Safety Assessments

- ***Ophthalmic Examination***: modification of Appendix 3 to include more information on the ophthalmic examination, including guidance that patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the Grade 1-4 scale.
  - **Modified Sections:** Table 1-1, Sections 9.2.1, 9.2.6, and 10.5, and Appendix 3.
  - **Rationale:** Changes were made to clarify acceptable assessment methods and specify the grading for patients enrolled under a prior version of the protocol who had detectable cataracts.
- CCI [redacted]

[redacted]

Supportive Care

- Removal of specific recommendation for dexamethasone (or equivalent glucocorticoid) as a recommended supportive care agent.
    - **Modified Sections:** Table 12-2, Sections 12.3.2.2 and 12.3.3.1.
    - **Rationale:** Rather than providing a specific recommendation for dexamethasone or equivalent to address fatigue or other selinexor-associated side effects, investigators are referred to broader NCCN guidelines (e.g., for fatigue) and their institutional guidelines. These recommendations provide more flexibility to investigators regarding management of fatigue or other selinexor-associated side effects in their patients.

Adverse Events

- Modified pregnancy text to replace text relating to a drug-drug interaction (i.e., pregnancy due to study drug reduction of the effectiveness of a contraceptive medication) with text relating to adverse events (i.e., medical occurrence observed in the mother or fetus/newborn).
    - **Modified Section:** 13.1.4.
    - **Rationale:** Change was made to improve accuracy.

Serious Adverse Event Reporting

- Revised contact information, updated overdose text, and modified description of SAE reporting requirements were added.
    - **Modified Sections:** List of Abbreviations, Sections 13.1.2, 13.1.3, 13.1.4, 13.1.5.1, and 15.11.2.
    - **Rationale:** These changes were made to reflect the transfer of pharmacovigilance responsibility from Clinipace Worldwide (CPWW) to Karyopharm Therapeutics, and to incorporate safety information from the Selinexor/KPT 330 IB v 4.0 (April, 2015) and minor changes to the description of SAE reporting procedures.

Amendment 4, Protocol Version 4.0

Version 4.0 incorporates changes to Version 3.0

Amendment Rationale

The major changes in this amendment of the protocol are as follows:

- Increase in the assumed drop out rate to ~20% to align with the actual rate at study sites and increase in the sample size to 170 patients to maintain power with the increased drop out rate.
- Addition of interim analysis after 25% of Overall Survival events in order to assess for early futility and prevent unnecessary exposure of patients to selinexor in the event futility is declared.
- Expansion of exclusion criteria to exclude patients with concurrent active malignancies that are not being treated.
- Addition of EQ-5D-5L Quality of Life questionnaire.
- Addition of 20 mg tablets in blister packs as an option for selinexor drug product.
- Removal of specific recommendation for the use of dexamethasone as a supportive care agent.

Other changes, primarily editorial and administrative, were made for readability and clarity. These changes include updates to data and corrections in the Synopsis, Schedule of Assessments, and body of the protocol for consistency and accuracy.

The revised protocol Version 4.0 dated 24 April 2015 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of the key changes that were made to Version 3.0 of the protocol, including the rationale for these changes, in Version 4.0 is provided below.

Changes to the protocol

Administrative Changes

- Internal changes to improve clarity and eliminate inconsistencies between sections; updated Table of Contents and hyperlinks (**Modified sections**: Global).
- Updated the version number and date of protocol from Version 3.0 dated 25 November 2014 to Version 4.0 dated 24 April 2015 (**Modified sections**: Global).
- Updated references and patient and incidence data (Modified sections: Global).

Clinical Experience

- ***AML efficacy and safety data:*** Section describing efficacy and safety data from AML patients treated with selinexor in Phase 1 study KCP-330-001 was updated based on information in the Selinexor/KPT-330 IB v 4.0 (April, 2015).
  - **Modified Section:** Section 4.3.
  - **Rationale:** To present currently available efficacy and safety data from AML patients treated with selinexor.
- ***Potential Risks:*** Side effects were updated based on information in the Selinexor/KPT-330 IB v 4.0 (April, 2015).
  - **Modified Section:** Section 4.3.1.
  - **Rationale:** To present currently available safety data for patients treated with selinexor.
- ***Reproductive Risks:*** Modified section to include summary of animal reproductive toxicity findings and statement that, as human reproductive risks are not known, all patients must use effective contraception as defined in Section 12.3.3.1 – Prevention of Pregnancy.
  - **Modified Section:** Section 4.3.1.1 (new section heading).
  - **Rationale:** Former language in this section only dealt with risk mitigation (contraception) without describing existing reproductive toxicity data.

Rationale for Dosing

- Addition of maximum allowable dose.
  - **Modified Sections:** Sections 5.1 and 12.3.1.5.
  - **Rationale:** To ensure no patient exceeds the maximum allowable dose.

Discontinuation Criteria

- Addition of End of Study section.
  - **Modified Sections:** Table 1-1, Section 11.3 (new sub-section).
  - **Rationale:** Provide definition of End of Study.

Study Design

- Increase in the assumed drop out rate from ~10% to ~20% and increase in the sample size from 150 patients to 170 patients.
  - **Modified Sections:** Synopsis, Sections 8.1, 9.1, and 14.1.2.
  - **Rationale:** Align with the actual drop out rate at the study sites and maintain power with the increased drop out rate.
- Addition of an interim analysis after 25% of Overall Survival events.
  - **Modified Sections:** Synopsis, Sections 7.2, 11.1, 14.1.2, and 14.2.1.4.
  - **Rationale:** Assess for early futility and prevent unnecessary exposure of patients to selinexor in the event futility is declared.
- Addition of BSA assessment at Days 1 and 15 of Cycles 2-5.
  - **Modified Sections:** Section 9.2.4 and Table 1-1.
  - **Rationale:** To ensure that none of the selinexor doses result in a dose > 70 mg/m^2.

- Increase in the anticipated enrollment period from 12 months to approximately 15-18 months.
    - **Modified Sections:** Synopsis and Section 14.1.2.
    - **Rationale:** Provide realistic timeframe for enrollment of additional patients.
- Clarification that patients who elect not to initiate study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained.
    - **Modified Sections:** Synopsis, Sections 7.1 and 11.2.
    - **Rationale:** Encourage patients who are randomized to physician's choice to provide follow-up information even if they choose not to initiate study treatment.
- Clarification of procedure for handling missing data for patients who are randomized but do not initiate study treatment.
    - **Modified Section:** Section 14.3.7.
    - **Rationale:** To account for missing data for randomized patients who do not receive study treatment.

Exclusion Criteria

- Expansion of exclusion criteria to exclude patients with concurrent active malignancies that are not being treated.
    - **Modified Section**: Section 8.4.
    - **Rationale:** To avoid compromising the objectives of the trial. Certain malignancies (e.g., CLL or prostate cancer), even if untreated, could compromise the trial objectives.

Treatment

- Addition of description of 20 mg selinexor tablet formulation, packaging and administration.
    - **Modified Sections**: Sections 12, 12.2.1, and 12.2.2.
    - **Rationale:** Change reflects pending addition of 20 mg selinexor tablets in blister packs as an additional form of selinexor drug product.
- Addition of new sub-section on Dose Modifications and Dose Delay (Section 12.3.1) to clarify criteria for dose modifications and discontinuation of patients due to dose delay.
    - **Modified Section:** Section 12.3.1 (new sub-section).
    - **Rationale:** Update of previous text to provide additional information and to improve clarity.
- Clarifications on restrictions on use of acetaminophen and GSH-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products.
    - **Modified Sections:** Section 12.3.4, Appendix 8.
    - **Rationale:** Minor revisions to improve clarity.
- Revision of Treatment Compliance (Section 12.5)
    - **Modified Section:** Section 12.5
    - **Rationale:** Update of previous text to provide additional information and to improve clarity.

Safety Assessments

- ***Ophthalmologic Examination***: modification of Appendix 5 to include more information on the ophthalmologic examination, provide additional detail regarding methods for assessment of visual acuity (i.e., Snellen's Equivalent based on either Snellen chart or ETDRS chart), and replace the Lens Opacities Classification System III grading system for cataracts with a Grade 1-4 grading system modified from the Optometric Clinical Practice Guideline: Care of Adult Patient with Cataract.
  - **Modified Sections:** Table 1-1, Section 9.2, Section 10.5, and Appendix 5.
  - **Rationale:** Changes were made to clarify acceptable assessment methods and replace the grading system for cataracts with a system that is more familiar to many ophthalmologists and optometrists.
- CCI [redacted]

Supportive Care

- Removal of specific recommendation for dexamethasone (or equivalent glucocorticoid) as a recommended supportive care agent.
  - **Modified Sections:** Table 12-2, Sections 12.3.2.2 and 12.3.3.1.
  - **Rationale:** Rather than providing a specific recommendation for dexamethasone or equivalent to address fatigue or other selinexor-associated side effects, investigators are referred to broader NCCN guidelines (e.g., for fatigue) and their institutional guidelines. These recommendations provide more flexibility to investigators regarding management of fatigue or other selinexor-associated side effects in their patients.

Serious Adverse Event Reporting

- Revised contact information, updated overdose text, and modified description of SAE reporting requirements were added.
  - **Modified Sections:** List of Abbreviations, Sections 13.1.2, 13.1.3, 13.1.4, 13.1.5.1, and 15.11.2.
  - **Rationale:** These changes were made to reflect the transfer of pharmacovigilance responsibility from Clinipace Worldwide (CPWW) to Karyopharm Therapeutics, and to incorporate safety information from the Selinexor/KPT 330 IB v 4.0 (April, 2015) and minor changes to the description of SAE reporting procedures.

AMENDMENT 3, VERSION 3.0

RATIONALE FOR THIS AMENDMENT

The purpose of this protocol amendment is to:

1. address feedback from study investigators regarding use of hydroxyurea and timing of dosing days and screening bone marrow aspirate,
2. remove the restriction on acetaminophen except on days of selinexor dosing (≤ 1 gm total daily dose of acetaminophen) and to add restriction on products that may alter selinexor metabolism
3. update the supportive care guidance and selinexor dose adjustment information, as well as study procedures including ophthalmological exam,
4. standardize reporting requirements for cerebellar toxicities (expand reporting beyond FDA and the Medicines and Healthcare Products Regulatory Agency as in Version 2.1), and
5. incorporate minor sponsor-initiated changes to the protocol to improve clarity.

SUMMARY OF CHANGES

Administrative and typographical corrections were made as needed throughout the document. The substantive changes include:

1. Modification of hydroxyurea use during the study
2. Modification of coagulation parameters
3. Modification of acetaminophen use and restrictions on drugs affecting glutathione-medicated metabolism
4. Clarification of options for selinexor twice weekly dosing days
5. Updated ophthalmologic exam procedures and required timing
6. Minor corrections to Complete Serum Chemistry assays
7. Bone marrow aspirate: expanded screening window under certain circumstances
8. CCI [redacted]
9. Updated Supportive Care and Dose Adjustment sections, including a new Supportive Care/Dose Adjustment table and two new Appendices
10. Clarified requirements for reporting cerebellar toxicities to regulatory authorities
11. Combined Rationales and Summaries of Changes for all amendments into a single Appendix

Each of these changes is described in detail below.

DESCRIPTION OF CHANGES

1. Modification of hydroxyurea use during the study

   Change: Old text indicated that hydroxyurea could only be used during Cycle 1. Protocol has been modified to allow hydroxyurea use at any time during the study but only in patients with WBC ≥30,000/μL.

   Rationale: This change was made after discussions with study investigators regarding the appropriate use of hydroxyurea in this study.

   Modified Sections: Synopsis, Section 7.1: Study Design Overview

2. Modification of coagulation parameters

   Changes: Inclusion criterion #10 was modified to indicate that PTT elevation for known lupus anticoagulant is allowed. In addition, protocol has been modified to allow Thromboplastin Time for assessment of coagulation if necessary.

   Rationale: These changes were made because 1) the specified requirement for PTT≤1.5 ULN is not relevant for patients with lupus anticoagulation and 2) certain sites routinely use TT for coagulation testing and requested permission to use this method.

   Modified Sections: Table 1-1: Schedule of Assessments and Study Activities, Table and footnote 15; Section 8.3: Inclusion Criteria; Section 10.5: Safety Assessments

3. Modification of acetaminophen use and restrictions on drugs affecting glutathione-medicated metabolism

   Changes:

   - *Modification of restriction on use of acetaminophen*: Patients should minimize the use of products containing acetaminophen (paracetamol) on the days of selinexor dosing. Acetaminophen (paracetamol) alone or in combination should not be taken within 2 hours before or after selinexor dosing. *New text***:** Although acetaminophen (paracetamol) use in combination with selinexor was restricted in previous selinexor studies based on theoretical interactions with GSH, ongoing clinical safety evaluations on the use of these drugs together have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen of up to 1 gm and selinexor up to 55 mg/m^2 (approximately 80-100 mg). Therefore, there are no longer any restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, EXCEPT on days on selinexor dosing, when acetaminophen must not exceed a total daily dose of 1 gram.
   - Addition of restrictions on glutathione (GSH)-, S-adenosylmethionine (SAM), or N-acetylcysteine (NAC)-containing products (potentially enhance selinexor metabolism) and addition of list of representative products (Appendix 6).

   Rationale: Ongoing clinical safety evaluations on the use of selinexor in combination with acetaminophen have not shown any significant clinical or laboratory abnormalities with doses of acetaminophen up to 1 gram and selinexor up to 55 mg/m^2

(approximately 80-100 mg). However, in comments on another selinexor clinical protocol, the FDA requested that acetaminophen use be restricted to 1 gm total daily dose on days of selinexor dosing. Restrictions on drugs that may enhance selinexor metabolism reflect the primary mechanism of selinexor metabolism by glutathione conjugation. The list of glutathione (GSH)-, S-adenosylmethionine (SAM), or N-acetylcysteine (NAC)-containing products added as a new Appendix (Appendix 6) was requested by the FDA.

Modified Sections: Synopsis; Section 9.2.11: Restrictions and Precautions; Section 12.3.4: Prohibited Medications

4. Clarification of options for selinexor dosing days

   Change: Added "e.g.," before description of possible twice weekly dosing days, to indicate that the list is not all inclusive.

   Rationale: This change was made to provide clinical sites more flexibility to schedule patient dosing days, including option to dose on Saturday or Sunday.

   Modified Sections: Synopsis; Section 5.1: Rationale for the Doses and Dosing Regimen; Section 12.2.3: Dosing Information

5. Updated ophthalmologic exam procedures and required timing

   Change: Removal of the visual field exam and requirement for all patients with cataracts at screening to be assessed every 3 months. Addition of requirement to grade any cataracts seen during exam using Lens Opacities Classification System III (included as new Appendix 3).

   Rationale: Changes were made following discussion with ophthalmologic expert regarding appropriate parameters to include in the exam, and appropriate frequency of assessment for all patients to effectively monitor for ophthalmological adverse events. All patients are assessed at screening and the Final Visit, and as clinically indicated at any time during the study.

   Modified Sections: Table 1-1: Schedule of Assessments and Study Activities, Table and footnote 8; Section 9.2: Description of Study Days; Section 10.5: Safety Assessments; Appendix 3: Lens Opacities Classification System III.

6. Bone marrow aspirate: expanded screening window under certain circumstances

   Change: Expanded window for bone marrow aspirate/biopsy during screening to within 14 days of Day 1 of Cycle 1, after consultation with, and approval by, the sponsor. In addition, text was added within Schedule of Assessments table clarifying timing of bone marrow aspirates during the study.

   Rationale: Change requested by investigators, as the expanded window may occasionally be required for certain patients.

   Modified Sections: Table 1-1: Schedule of Assessments and Study Activities, Table and footnote 16; Section 9.2.1: Visit 1 (within 14 days prior to start of therapy); Screening #1.

7. Minor corrections to Complete Serum Chemistry assays

   Change: Changed "urate" to "uric acid" and "amylase" to "pancreatic amylase" in Complete Serum Chemistry.

   Rationale: Changes made to clarify assays to be performed.

   Modified Sections: Table 1-1: Schedule of Assessments and Study Activities, Table and footnote 13; Section 10.5: Safety Assessments.

CCI [redacted]

9. Updated Supportive Care and Dose Adjustment sections, including a new supportive care/dose adjustment table and two new Appendices

   Changes:

   - Replaced Table 12-2: Dose Adjustment Guidelines for Non-Hematologic Selinexor-Related Toxicities with new Table 12-2: Supportive Care and Dose Adjustment Guidelines for Non-Hematologic Selinexor-Related Toxicities.
   - Added new Section 12.2.5.1: Selinexor Dose Adjustments for Hematological Toxicities.
   - Minor update to Conditions not Requiring Selinexor Dose Adjustment.
   - Changed title of "Concomitant Treatment" section to "Supportive Care and Concomitant Treatment" and moved this section from 12.4 to 12.3.

- Removed prophylactic therapy section and replaced with new sections (12.3.1 and 12.3.2) describing required and recommended supportive care
- Removed supportive care guidance text from the body of the protocol that is now included in Table 12-2.
- Addition of two supportive care Appendices: Appendix 4: NCCN Clinical Practice Guidelines in Oncology: Antiemesis and Appendix 5: NCCN Clinical Practice Guidelines in Oncology: Anorexia/Cachexia.

Rationale: Changes reflect current recommendations for management of selinexor-related adverse events, based on results from ongoing Phase 1 and Phase 2 clinical studies. Section 12 was re-ordered and supportive care and dose adjustment guidances were consolidated into a single table to improve clarity and flow of adverse event management sections. Appendices were added to provide investigators with additional AE management guidance.

Modified Sections: Synopsis; Section 12.2.4: Dosing Information for Study Participants; Section 12.3: Dose Reduction Guidelines; Section 12.3.1.1: Selinexor Dose Adjustments for Hematological Toxicities; Section 12.3.2: Supportive Care and Concomitant Treatments; Section 12.3.2.1: Required Supportive Care Medications; Section 12.3.2.2: Supportive Care Recommendations for Selinexor-Related Adverse Events.

10. Clarified requirements for reporting acute cerebellar syndrome to regulatory authorities

Change: Updated requirement for reporting of all cases of cerebellar toxicities to include not only FDA and MHRA (as in Version 2.1) but also Health Canada or other appropriate national regulatory body.

Rationale: FDA and MHRA had requested specific reporting requirements for cerebellar toxicities. Change made to standardize global reporting of cerebellar toxicities.

Modified Sections: Section 13.1.5.1 (Adverse Event) Reporting Requirements.

11. Combined Rationales and Summaries of Changes for all amendments into a single Appendix

Change: Prior versions of the protocol had separate Summary of Change appendices for each amendment. All Summaries of Changes are now combined in Appendix 6: Protocol Amendments: Rationales and Summaries of Changes. Amendment summaries are presented in reverse chronological order, starting with most recent amendment

Rationale: Simplify the protocol by including history of changes in one Appendix.

Modified Section: Appendix 6.

AMENDMENT 2, VERSION 2.1 (UK-Specific; submitted only to MHRA)

RATIONALE FOR THIS AMENDMENT

The purpose of this protocol amendment is to address a comment received after review of the protocol by the Medicines and Healthcare Products Regulatory Agency.

This change is:

- All cases of cerebellar toxicities of grade 3 or higher will also be reported to the MHRA in an expedited manner within 7 days of the Sponsor, or designee, being notified of the event.

Specific changes are displayed in **Boldface**.

Section 13.1.5.1 Reporting Requirements

Unexpected serious suspected adverse reactions are subject to expedited reporting to FDA. ALL SAEs must be entered into the eCRF and reported to the Sponsor within 24 hours of first knowledge of the event by study personnel. In addition, all cases of cerebellar toxicities of grade 3 or higher must be captured as an SAE and reported to the FDA **and the MHRA (Medicines and Healthcare Products Regulatory Agency)** in an expedited IND Safety Report within 7 days of the event.

AMENDMENT 1, VERSION 2.0

RATIONALE FOR THIS AMENDMENT

The purpose of this protocol amendment is to address comments received from regulatory authorities and ethical committees following review of protocol Version 1 dated 21 January 2014.

Given that thrombocytopenia is expected in patients with this protocol regimen, it was recommended that the treatment goal for hypertension should be lower than BP = 150/100 mmHg, the original protocol limit, to reduce the risk of CNS bleeding. This observation is addressed in Section 3: Change 1. Additionally, it was recommended that the efficacy analysis be conducted in the intent-to-treat (ITT) population (all patients randomized; whether dosed or not) as opposed to the modified intent-to-treat (mITT) population described in the original protocol. This change in analysis methodology is addressed in Section 3: Change 5.

Other changes included in this amendment are described in the approximate order they appear in the protocol in Changes $\geq$ 2. When a protocol change applies to multiple protocol sections, the later sections are identified where similar edits were applied.

Minor sponsor-initiated changes were also made to the protocol for clarity. Administrative and typographical corrections were made as needed throughout the document. Clinical data from ongoing clinical studies have been updated as available throughout the protocol.

Section numbers are provided for old text in protocol Version 1.0 dated 21 January 2014 and for amended text or added text in the protocol Version 2.0 dated 03 July 2014.

SUMMARY OF CHANGES

The substantive changes addressed in the following order include:

1. Hypertension blood pressure (BP) treatment goal
2. Clarification of dosing schedule options
3. Revised description of third physician's choice best supportive care (BSC) + hypomethylating agent
4. Change from a 4-hour to a 2-hour window between administration of selinexor and acetaminophen (paracetamol)-containing medications
5. Change in analysis from mITT patient population to ITT population
6. Additions to the "Schedule of Assessments and Study Activities"
    a. Added Randomization with criteria to Visit 3
    b. Addition of Cycle 1 Day 3 only phone contact with patient to monitor AEs and concomitant medications
    c. Addition of 30-Day (after Final Visit) and Survival patient contacts
7. Updated side effects information
8. Update to Rationale for Dosing and the Dosing Regimen
9. Deletion of instructions for patients who achieve CR and rationale for change

10. Change in storage temperatures for selinexor
11. Update in description of prophylactic therapy instructions for AEs
12. Update in FDA guidance for reporting serious adverse events (SAEs)
13. CCI [redacted]
14. Updated supportive care for liver enzyme increase
15. Updated Prohibited Medication information
16. Addition of Appendix 2: International Working Group Guidelines for AML

DESCRIPTION OF CHANGES

CHANGE 1: SECTION 12.3 DOSE REDUCTION GUIDELINES

Old text: In

Table 12-2 contains supportive care and selinexor dose adjustment guidelines for non-hematologic selinexor-related toxicities. Additional supportive care guidance can be found in Section 12.3.2.

Table 6 contains supportive care and selinexor dose adjustment guidelines for non-hematologic selinexor-related toxicities. Additional supportive care guidance can be found in Section 12.3.2.

***Dose Adjustment Guidelines for Non-Hematologic Selinexor-Related Toxicities*, Cardiac (rare), Hypertension, Grades 2/3 and 4.** Selinexor may be restarted in conjunction with standard antihypertensive medication if BP is controlled (i.e., BP < 150/100 mmHg).

has been addressed as follows:
In this amended protocol, we have removed the recommendation for treatment of hypertension and, therefore, the study sites may use their standard protocols. We have no evidence that selinexor contributes to hypertension.

CHANGE 2: PROTOCOL SYNOPSIS, DOSING SCHEDULE OPTION

Old Text: Protocol Synopsis, Test Product, Dose and Mode of Administration
Selinexor (KPT-330) will be given initially at an oral fixed dose (equivalent to ~55 mg/m^2) twice weekly (Monday and Wednesday or Tuesday and Thursday).

has been changed to:
Selinexor (KPT-330) will be given initially at an oral fixed dose (equivalent to ~55 mg/m^2) twice weekly (Monday and Wednesday or Tuesday and Thursday or Wednesday and Friday).

Similar text changes that describe this additional dosing schedule option given to patients have been made in Section 5.1: Rationale for the Doses and the Dosing Regimen, Section 7.1: Study Design Overview, and in Section 12.2.3: Dosing Information.

CHANGE 3: PROTOCOL SYNOPSIS, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION

Old Text: Reference Therapy, Dose and Mode of Administration
(3) BSC + hypomethylating agent: azacitidine 75 mg/m^2 by sc injection daily on Days 1-7 (7 doses) to be repeated at 28 day intervals, *or* decitabine (20 mg/m^2 IV over 1 hour daily on Days 1-5 to be repeated at 28 day intervals).

has been changed to:
(3) BSC + hypomethylating agent: azacitidine 75 mg/m^2 by sc injection daily on Days 1-7 or 1-5, 8, 9 (7 doses) to be repeated at ≥28 day intervals, *or* decitabine (20 mg/m^2 IV over 1 hour daily on days 1-5 or days 1-10 to be repeated at ≥28 day intervals). This identical change was made in Section 7.1: Study Design Overview and in Section 12.1: Dosing and Administration of Physician Choice's Study Medication (Reference Therapy).

CHANGE 4: PROTOCOL SYNOPSIS, CONCOMITANT MEDICATIONS

Old Text: Protocol Synopsis, Concomitant Medications
Acetaminophen (paracetamol) should not be taken within 4 hours before or after selinexor dosing,

has been changed to:
Acetaminophen (paracetamol) alone or in combination should not be taken within 2 hours before or after selinexor dosing.

Similar text revisions reflecting the change in the dosing window for acetaminophen (paracetamol) products have been made in Section 9.2.11: Restrictions and Precautions, in Section 12.3.3: Concomitant Medication and Treatment and in Section 12.3.4: Prohibited Medication.

CHANGE 5: PROTOCOL SYNOPSIS, STATISTICAL METHODS

Old Text: Study Synopsis, Criteria for Evaluation, Efficacy
The analysis of OS will be performed on the modified intent-to-treat (mITT) population as the primary analysis, and on the per-protocol (PP) population as a supportive analysis.

has been changed to:
The analysis of OS will be performed on the intent-to-treat (ITT) population as the primary analysis, and on the per-protocol (PP) population as a supportive analysis

<u>This significant change has also been made in the following protocol locations:</u>

Old Text: Protocol Synopsis, Statistical Methods
The modified intent-to-treat population (mITT) will consist of all patients who are randomized to, and receive at least one dose of, study therapy. This population will be used for primary analyses of efficacy.

has been changed to:
The intent-to-treat population (ITT) will consist of all patients who are randomized to study therapy. This population will be used for primary analyses of efficacy.

Old Text: Statistical Methods, Section 14.2.1.1: Modified Intent-To-Treat Population
The modified intent-to-treat population (mITT) will consist of all patients who are randomized and receive at least one dose of study therapy. This population will include patients with at least one dose of study drug who have discontinued therapy due to toxicity or disease progression and patients who have taken at least one dose of study drug and have died from any cause related to study drug or disease. This population will be used for primary analyses of efficacy.

has been changed to:
The intent-to-treat population (ITT) will consist of all patients who are randomized to study therapy. This population will include patients who have discontinued therapy due to toxicity or disease progression and patients who have died from any cause related to study drug or disease. This population will be used for primary analyses of efficacy, and such analyses will be based on the randomized treatment assignment.

Old Text: Statistical Methods, Section 14.2.1.2: Per-Patient Population
This population will be used for supportive inferences concerning efficacy; however, if there are major differences between the results in this population and those obtained in the mITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.

has been changed to:
This population will be used for supportive inferences concerning efficacy; however, if there are major differences between the results in this population and those obtained in the ITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.

Old Text: Statistical Methods, Section 14.2.1.3: Safety Population
The safety population will consist of all patients who have received any amount of study medication; it is anticipated this population consist of the same patients as in the mITT population.

has been changed to:
The safety population will consist of all patients who have received any amount of study medication; analyses of safety will be performed based on treatment received, even if different from that randomized.

CHANGE 6: ADDITIONS TO THE "SCHEDULE OF ASSESSMENTS AND STUDY ACTIVITIES"

The following additions have been made in the "Schedule of Assessments and Study Activities" and corresponding sections in the body of the protocol.

The table title has been changed to "Table 1-1: Schedule of Assessments and Study Activities" for easier reference throughout the amended protocol.

- Added Randomization Visit 3 with this footnote: Randomization must occur ≤3 calendar days of Cycle 1 Day 1

- Added "Nutritional consultation" procedure to Table 1-1 as described in Footnote 22: It is strongly recommended that patients be given nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor. This addition is similarly documented in Study Plans and Procedures, Section 9.2.2: Screening Visit 2.

- Added another column to Table 1-1 for a telephone contact on Day 3 of Cycle 1 as well as a new Footnote 23 which reads "Cycle 1 Day 3 phone call with patient to evaluate supportive care medications and adverse events, and to adjust supportive care as appropriate. The phone contact with the patient must take place on Day 3 following the Cycle 1 Day 1 selinexor dosing". The footnotes thereafter were re-numbered accordingly. This addition is similarly documented in Study Plans and Procedures, Section9.2.4: Cycle 1 Day 3 only.

- Added a "30-Day Safety Follow-up Visit" procedure in Table 1-1 as described in Footnote 24: By phone (or a visit, if possible), assess overall medical condition of the patient and status of his/her AML, follow-up on any AEs that were not resolved at the Final Study Visit, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment. This addition is similarly documented in Study Plans and Procedures, Section 9.2.9: 30 Day Patient Safety Follow-up.

- Added a "Survival Follow-up Visit" procedure in Table 1-1 as described in Footnote 25: After study discontinuation, a call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's AML status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment. This addition is similarly documented in Study Plans and Procedures, Section 9.2.10: Survival Follow-up

- Edited and clarified instructions about Complete and Limited Serum Chemistries on timing and inclusion of TSH in Table 1-1 Footnotes 12 and 13 and in Methods of Assessments and Endpoints, Section 10.5: Safety Assessments, Serum Chemistry and to allow for the collection of either Blood Urea Nitrogen (BUN) or urea to accommodate institutions that do not analyze BUN but do analyze urea as documented in Footnotes 12 and 13 and in Section10.5.

CHANGE 7: SECTION 4.3 CLINICAL EXPERIENCE

Old Text: Clinical Experience, Section 4.3.1, Potential Risks
Side effects observed in patients include:

Most common side effects:

- nausea
- loss of appetite
- fatigue
- vomiting
- weight loss

Less common:

- diarrhea
- change in taste
- changes in vision including blurred vision
- low platelets without bleeding
- decrease in red blood cells
- low sodium

Rare (< 5%):

- worsening of existing cataracts
- elevated levels of bilirubin
- elevated levels liver enzymes (ALT and AST)

has been changed to

Side effects observed to date in patients are shown below. Please see *KPT-330 for Oral Administration Investigator's Brochure* for most up-to-date information.

Most common side effects:

- nausea
- loss of appetite
- fatigue
- vomiting
- weight loss
- diarrhea

Less common:

- change in taste
- changes in vision including blurred vision
- low platelets
- decrease in red blood cells
- low sodium without symptoms

Rare (< 5%):

- worsening of pre-existing cataracts
- elevated levels of bilirubin
- elevated levels of liver enzymes (ALT and AST)

One patient, heavily pre-treated for recurrent pancreatic cancer, developed, 'acute cerebellar syndrome' following 4 doses of KPT-330 at 85 mg/m twice weekly. The patient experienced abnormal speech, loss of coordination, and was unable to walk. No other patients have reported such symptoms to date.

CHANGE 8: SECTION 5: RATIONALE FOR THE STUDY

Old Text Section 5.1: Rationale for Dosing and the Dosing Regimen
Dose escalation on this twice-weekly schedule in KCP-330-001 in patients with B-cell malignancies is currently proceeding at 60 mg/m^2 and in patients with rel/ref AML at 70 mg/m^2.

has been changed to:
A MTD of 65 mg/m^2 twice weekly (Days 1 and 3) has been determined in the ongoing Phase 1 study of selinexor in patients with advanced solid tumors (KCP-330-002). Two dose-limiting toxicities (DLTs) occurred in 2 patients in the solid tumor study (KCP-330-002) treated at 85 mg/m^2 twice weekly and included 'probably related' asymptomatic Grade 3 hyponatremia and 'possibly related' acute cerebellar syndrome with ataxia and dysarthria. Of note, asymptomatic hyponatremia had been observed in other patients treated with selinexor, but only this one case of central nervous system (CNS) toxicity was observed across any of the selinexor trials (>300 patients as of 15 May 2014)

CHANGE 9: SECTION 12.2: DOSING AND ADMINISTRATION OF SELINEXOR

Old Text: Section 12.3: Dosing Instructions for Patients who Achieve CR (see below) has been deleted.
"For patients who achieve CR or CRi for ≥ 8 weeks (including two bone marrow [BM] biopsies confirming CR/CRi), dosing frequency may be reduced to once weekly at the same dose based on the treating Physician recommendation and following consultation with the Sponsor. In the event that patients show early evidence of relapse from CR or CRi, twice weekly dosing frequency may be reinstated."

The rationale for this change is that because of emerging data from the ongoing Phase 1 study, the physician can choose to reduce the dose based on dose modification guidelines.

CHANGE 10: SECTION12.4: SELINEXOR STORAGE AND ACCOUNTABILITY

Old Text: Treatment, Section 12.4, Selinexor Storage and Accountability
Selinexor tablets will be stored at ambient or refrigerated temperatures between (36-86°F) or (2-30°C) in a locked and secured area with restricted access to study staff.

has been changed to:
Selinexor tablets will be stored at ambient or refrigerated temperatures between (41-86°F) or (5-30°C) in a locked and secured area with access restricted to study staff.

This change documents a narrower temperature range in cold temperatures for best storage of selinexor.

CHANGE 11: SECTION 12.3.2: RESCUE MEDICATIONS AND CONCOMITANT TREATMENTS

Old Text: Treatment, Section 12.3.2.1, Required Prophylactic Therapy for Adverse Events Associated with Selinexor
All patients will receive prophylactic treatment to prevent anorexia, fatigue and nausea, which includes:

Megesterol acetate 160-400 mg daily, 0-3 days before the first dosing day of selinexor

OR
Dexamethasone 2-4 mg (or equivalent steroid) on days of dosing and the following day. Dexamethasone may be given prior to initiation of dosing or more frequently as needed

AND

Olanzapine 2.5-5.0 mg qhs or 2.5 mg bid, 0-3 days before the first dosing day of selinexor

OR

Mirtazapine 15 mg qd (qpm/phs), 0-3 days before the first dosing day of selinexor

has been changed to:
Two prophylactic medications (one from Group A and one from Group B shown below) must be used to minimize anorexia, nausea and fatigue and are required for Cycle 1, and may be tapered or discontinued after Cycle 2 as tolerated. If there is an adverse reaction to one of the prophylactic medications, it may be discontinued or omitted. In addition, medications from Group C and D may be used (optional).

A. **Dexamethasone** 12mg will be given on the days of selinexor dosing. All patients must receive dexamethasone unless they cannot tolerate it or it is contraindicated.

Optional: The day after selinexor dosing additional 4-8 mg dexamethasone (or equivalent glucocorticoid) may be given; maximum 40 mg dexamethasone or equivalent per week)

OR

Megesterol Acetate For patients with partial intolerance to glucocorticoids or for whom glucocorticoids are contraindicated (i.e., patients receiving < 4 mg dexamethasone on dosing days): patients must receive megesterol acetate 80-400 mg daily, starting 1-3 days before the first dosing day of selinexor.

Optional: In addition, megesterol acetate 80-400 mg daily can be added for any patients as part of general supportive care for anorexia.

B. **5-HT3 Antagonists (ondansetron** 8 mg or equivalent) starting before the first dose of selinexor and continued bid – tid prn.

C. **OPTIONAL:** Either **olanzapine (preferred)** 5.0 mg qhs or 2.5 mg bid, starting 0-3 days before the first dosing day of selinexor –or– **mirtazapine** 7.5-15 mg daily (qpm or qhs), starting 0-3 days before the first dosing day of selinexor. Please note that olanzapine and mirtazapine can induce fatigue and should be discontinued in the case for fatigue grade >2.

D. **OPTIONAL: Neurokinin 1 receptor antagonist (NK1R antagonist) (aprepitant** or equivalent**)** should be considered and will be covered for selected patients who have severe nausea and vomiting in the first 2 doses.

Table 12-3 Sample Weekly Schedule for Selinexor, Dexamethasone and Prophylactic Therapy

Compound	Day Prior to first Selinexor Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Selinexor		X		X				
Dexamethasone (12 mg)*		X		X				
Dexamethasone – optional (4-8 mg) or equivalent glucocorticoid			X		X			
Megesterol acetate – optional	X	X	X	X	X	X	X	X
5-HT3 Antagonist (e.g., ondansetron)		X	BID-TID prn					
Olanzapine or mirtazapine – optional	X	X	X	X	X	X	X	X
NK1R antagonist (e.g., aprepitant) – optional		X	BID-TID prn					

* For patients with partial intolerance to glucocorticoids, a minimum dose of 4 mg dexamethasone is permitted on dosing days.

CHANGE 12: SECTION 13.1.5: SERIOUS ADVERSE EVENT REPORTING

Old Text: Adverse Events, Section 13.1.5.1, Reporting Requirements
Unexpected serious suspected adverse reactions are subject to expedited reporting to FDA. ALL SAEs must be entered into the eCRF and reported to the Sponsor within 24 hours of first knowledge of the event by study personnel.

has been changed to:
Unexpected serious suspected adverse reactions are subject to expedited reporting to FDA. ALL SAEs must be entered into the eCRF and reported to the Sponsor within 24 hours of first knowledge of the event by study personnel. In addition, all cases of cerebellar toxicities of grade 3 or higher must be captured as an SAE and reported to the FDA in an expedited IND Safety Report within 7 days of the event.

Old Text: Adverse Events, Section 13.1.5.1, Reporting Requirements
Karyopharm, or their designee, is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA according to 21 CFR 312.32 and the draft guidance (2010) and other regulatory agencies according to country-specific guidelines.

has been changed to:
Karyopharm, or their designee, is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA according to 21 CFR 312.32 and applicable regulatory guidance documents and other regulatory agencies according to country specific guidelines. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Ethics committee (EC).

CHANGE 13: CCI [redacted]

CCI [redacted]

[redacted]

CHANGE 14: SECTION 12.4.2: SUPPORTIVE CARE

Old Text: Section12.4.2.7: Liver Enzyme Increase
To date, significant liver toxicity has not been reported in patients treated with selinexor. Patients should minimize their use of alcohol and acetaminophen (paracetamol) as these drugs may deplete hepatic glutathione that could alter selinexor metabolism. Glutathione (GSH) replacing agents such as N-acetylcysteine or S-adenosylmethionine may be considered if selinexor induced liver dysfunction is suspected

has been changed to:
To date, significant liver toxicity has not been reported in patients treated with selinexor. Patients should minimize their use of alcohol and acetaminophen (paracetamol) as these drugs may deplete hepatic glutathione that could alter selinexor metabolism.

Statement regarding glutathione replacing agents was removed as these agents could potentially influence selinexor metabolism and exposure in patients.

CHANGE 15: SECTION 12.3.4: PROHIBITED MEDICATION

Old Text: (Paragraph below)
The primary metabolism of selinexor in humans is through glucuronidation. Inactivation of selinexor by glutathione conjugation is a secondary metabolic pathway *in vitro* and *in vivo*, including in humans. This process can be mediated in the absence of proteins, indicating that it is thermodynamically favorable. *In vitro* studies using human liver microsomes confirm *in vivo* findings that selinexor undergoes minimal CYP450 metabolism. Therefore, administration of selinexor with drugs which undergo substantial glutathione conjugation should be minimized or avoided. These drugs include acetaminophen (paracetamol) and ethyl alcohol. It should be noted that studies of selinexor in combination with acetaminophen (paracetamol) are underway and preliminary data suggest the combination of low dose acetaminophen (paracetamol) and selinexor is not toxic. Therefore, these recommendations are empirical, and acetaminophen (paracetamol) should not be ingested 4 hours before through 4 hours after selinexor dosing. It should also be noted that recreational ethanol ingestion is associated with glutathione depletion; therefore, the use of products containing ethanol should be minimized or avoided on selinexor dosing days.

has been replaced by:
Use of products containing ethanol should be minimized or avoided on selinexor dosing days.

CHANGE 16: ADDITION OF APPENDIX 2: INTERNATIONAL WORKING GROUP GUIDELINES FOR AML

This new appendix has been added to provide convenient access to the revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for AML.