MSK PROTOCOL COVER SHEET

A Phase II Study of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with Myelodysplastic Syndromes

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Synopsis

Study Title:	A Phase II Study of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Patients with Myelodysplastic Syndromes
Primary Objective:	Best overall response rate (CR + marrow CR + PR + HI) of Selinexor in patients with myelodysplastic syndromes refractory to hypomethylating agents
Secondary Objectives:	• To determine response duration in patients with MDS who achieve a response of stable disease, HI, mCR, PR, CR. • To describe the frequency of Stable Disease • To describe survival of MDS patients receiving Selinexor after study enrollment • To assess the response rate and response duration in therapy-related MDS • To assess tolerability of chronic Selinexor therapy in patients with Myelodysplastic Syndromes • To determine the pharmacodynamics (PDn) of Selinexor
Study Design	• Single-center, non-randomized, open-label, single-arm phase II study of oral Selinexor • Patients with myelodysplastic syndromes who are refractory to hypomethylating agents (decitabine or 5-azacytidine) will receive oral Selinexor at a starting dose of 60mg twice weekly for 2 weeks, followed by 1 week of no therapy. o Dose reductions are permitted for patients who are benefiting from Selinexor but have poor tolerance • Pharmacodynamic studies will be obtained to study the effects of Selinexor on key signalling pathways which affect cellular growth and differentiation. Patients may continue Selinexor indefinitely, barring disease progression, excessive toxicity or patient, physican decision to terminate treatment.
Sample Size:	20 patients
Study Duration	With an estimated accrual rate of 1-2 patients per month, and a total number of 25 patients planned, the anticipated enrolment period will last 10-20 months.
Inclusion / Exclusion Criteria:	**Inclusions:** Patients must meet all of the following inclusion criteria to be eligible to enroll in this study.

	1. Written informed consent in accordance with federal, local, and institutional guidelines 2. Age ≥18 years 3. Patients with Myelodysplastic Syndromes refractory (primary or acquired resistance) to hypomethylating agents(decitabine or 5-azacytidine). At least 4 1-month cycles of prior decitabine or SGI-110 OR 6 1-month cycles of 5-azacytidine (IV, subcutaneous, or oral is required unless the patient has progressive disease prior to completing the required number of cycles. 4. Histologically confirmed diagnosis of a Myelodysplastic Syndrome, meeting criteria for any subtype in the FAB or WHO classification systems with any IPSS score. 5. Patients with MDS who relapse after allogeneic stem cell transplant are eligible if they received standard dose decitabine or 5-azacytidine prior to or after stem cell transplant as defined in inclusion criteria 3. 6. If patient has undergone prior allogeneic stem cell transplant, they must be greater than 100 days post transplant and have ≤ grade 2 graft-versus-host disease 7. There is no upper limit on the number of prior treatments provided all inclusion/exclusion criteria are met. 8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 (Appendix 1). 9. Patients receiving erythropoietin (darbepoetin, epoetin alfa) must be on a stable dose and with stable transfusion requirement or hemoglobin level during the 8 weeks prior to study entry. 10. Adequate hepatic function within 21 days prior to C1D1: total bilirubin <2 times the upper limit of normal (ULN), asparate aminotransferase (AST) <2.5 times ULN and alanine aminotransferase (ALT) <2.5 times ULN. 11. Adequate renal function within 21 days prior to C1D1: estimated creatinine clearance of ≥ 30 mL/min, calculated using the formula of Cockroft and Gault (140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female. 12. 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.

Exclusions:

1. Patients who are pregnant or lactating;
2. Chemotherapy or immunotherapy or any other anticancer therapy ≤3 weeks prior to cycle 1 day 1. Hydroxyurea may be continued until 72 hours prior to first dose and at least 24 hours before the baseline bone marrow aspiration is performed;
3. Major surgery within four weeks before Day 1;
4. Unstable cardiovascular function:
   - symptomatic ischemia, or
   - uncontrolled clinically significant conduction abnormalities (ie: ventricular tachycardia on antiarrhythmics are excluded and 1st degree AV block or asymptomatic LAFB/RBBB will not be excluded), or
   - congestive heart failure (CHF) of NYHA Class ≥3, or
   - myocardial infarction (MI) within 3 months;
5. Uncontrolled active infection requiring systemic antibiotics, antivirals, or antifungals within one week prior to first dose; Prophylactic antimicrobials are permitted.
6. Known to be HIV seropositive;
7. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface *antigen*);
8. Patients with another *active* malignancy. Asymptomatic sites of disease are not considered active. Treated or untreated sites of disease may be considered inactive if they are stable for at least 2 months and are not expected to require therapy for 4 months.
9. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea.
10. Grade ≥2 peripheral neuropathy at baseline.
11. History of seizures, movement disorders or cerebrovascular accident within the past 1 year prior to cycle 1 day 1.

	12. Patients with macular degeneration with markedly decreased visual acuity, or uncontrolled glaucoma. 13. Patients who are significantly below their ideal body weigh (BMI < 17). 14. Serious psychiatric or medical conditions that could interfere with treatment.
Pharmacodynamic Assessments:	Pharmacodynamic studies will be obtained to study the effects of Selinexor on signalling pathways which affect cellular growth and differentiation.
Efficacy Assessment	Efficacy will be assessed by evaluation of bone marrow aspirates and biopsies, complete blood counts, and transfusion records. Hematologic Improvement will be assessed continuously, with the use of CBC values and transfusion records. At the time of bone marrow aspirates and biopsies, full efficacy evaluations will be performed, taking into account blood and bone marrow parameters, and responses will be assessed using the 2006 Modified MDS International Working Group Response Criteria.
Safety Variables & Analysis:	The safety and tolerability of Selinexor and ST will be evaluated by means of drug related AE reports, physical examinations, and laboratory safety evaluations. Common Terminology Criteria for Adverse Events (CTCAE) V4.03 will be used for grading of AEs. Investigators will provide their assessment of causality as 1) unrelated, 2) possibly related, or 3) probably or definitely related for all AEs.
Statistical Analysis:	**Primary endpoint evaluation** The primary endpoint of this study is to investigate the efficacy of Selinexor in patients with MDS refractory to hypomethylating agents (decitabine and/or 5-azacytidine). The standard treatment in this setting is supportive care, where the response rate is assumed to be zero. Therefore, in this population, a response rate of 25% would be considered promising, whereas a 5% response rate would not be considered promising. For purposes of assessing the primary endpoint, response categories will include CR, PR, marrow CR (mCR), or Hematologic Improvement. Using a Simon's two-stage minimax design, this trial will accrue a maximum of 20 patients who receive study drug. Early termination may occur if no responses are observed in the first 13 patients. If at least one response is observed, the trial will continue to the maximum sample size. At the end of the trial, the treatment strategy will be considered promising in this patient population if at least 3 patients achieve a response. The type I and type II errors are set at 0.10. The response evaluation cohort will include those patients who have completed one cycle of therapy and have undergone at least one full scheduled post-treatment disease assessment (informative bone marrow aspirate or biopsy, cytogenetics, and

	CBC with differential) after 1 cycle of therapy. For patients who come off study after completing 1 cycle of therapy and are unable to undergo (or refuse) a bone marrow procedure, an assessment for Hematologic Improvement (based on CBC data) will be performed and described and an attempt will be made to obtain follow-up CBC data for the 8 weeks mandated to confirm Hematologic Improvement according to the MDS International Working Group response criteria. Patients who come off study after starting study drug because of toxicity, death, or withdrawal of consent prior to undergoing a response assessment will not be replaced and will be considered a treatment failure. Patients who enroll on study but do not receive study therapy will be replaced. **Analysis of secondary endpoints** Secondary efficacy endpoints include response duration, as well as an assessment of the incidence of Stable Disease, given the finding that Stable Disease is associated with a survival benefit in MDS patients receiving up-front therapy with 5-azacytidine. The response rate and response duration will also be described for the generally poor-risk therapy-related MDS patients enrolled on this study (therapy-related MDS accruals may approach ~ 50%, as seen in MSKCC protocol 06-054). Survival will be described as a secondary endpoint, and will be calculated from the time of study entry. Also, since Selinexor may require chronic dosing to maintain its effect, we will also describe the overall tolerability of chronic Selinexor dosing by summarizing safety data collected on patients throughout all cycles of treatment who have received at least 1 dose of Selinexor. Descriptive statistics will be used to explore the relationship between therapeutic response or study entry disease parameters, and the results of the pharmacodynamics studies.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- The primary objective is to determine the best overall response rate (CR + marrow CR + PR + HI) according to the modified MDS International Working Group response criteria (Cheson, 2006) of Selinexor in patients with myelodysplastic syndromes refractory to hypomethylating agents

Secondary Objectives:

- To determine response duration in patients with MDS who achieve a response of stable disease, HI, mCR, PR, CR.
- To describe the frequency of Stable Disease
- To describe survival of MDS patients receiving Selinexor after study enrollment.
- To assess the response rate and response duration in therapy-related MDS

- To assess tolerability of chronic Selinexor therapy in patients with Myelodysplastic Syndromes.
- To study the pharmacodynamics (PDn) of Selinexor.

3.0 BACKGROUND AND RATIONALE

Cancer cells must inactivate their tumor suppressor proteins (TSPs) in order to perpetuate their neoplastic phenotype. TSPs require nuclear localization in order to function. Like most proteins, TSPs are shuttled into the nucleus by carrier proteins called importins, and they are carried out of the nucleus by exportins. Exportin 1 (XPO1), also called CRM1, is one of seven major nuclear exporters responsible for carrying ~220 cargo proteins out of the nucleus into the cytoplasm. Nearly all TSPs are transported out of the nucleus exclusively by XPO1. Furthermore, XPO1 is overexpressed by 2-4 fold in nearly all cancer cells, and its levels correlate with poor prognosis and/or chemotherapy resistance. Current research suggests that cancer cells have co-opted XPO1 in order to neutralize their TSPs.

Selinexor (KPT-330) is a small molecule, drug-like, orally available Selective Inhibitor of Nuclear Export (SINE) compound that is a slowly reversible covalent antagonist of XPO1. By blocking XPO1, Selinexor induces the accumulation of TSPs in the cell nucleus, leading to activation of their tumor suppressing function. Cells with marked genomic (DNA) damage, including cancer cells, undergo apoptotic cell death; normal cells, with little or no genomic damage, undergo transient, reversible cell cycle arrest. Consistent with its novel mechanism of broadly inducing TSP function, Selinexor has shown broad anti-tumor in preclinical mouse models and spontaneous canine cancers. Selinexor is currently being studied in three Phase 1 clinical trials in patients with advanced hematolgic or solid tumor malignancies, or in patients with treatment refractory sarcomas. Preliminary evidence of anti-tumor activity in humans with a diverse set of cancers formed the basis for studying the effect of Selinexor on patients with MDS.

3.1 Selinexor: Mechanism of Action and Preclinical Summary

A brief summary of key aspects the preclinical evaluation of Selinexor is presented below. Further detailed information is provided in the Investigator's Brochure.

Selinexor is an orally available, irreversible, potent and Selective Inhibitor of Nuclear Export (SINE) that specifically blocks XPO1. Selinexor restores many of the TSP and other growth regulatory proteins to the nucleus where they can carry out their normal functions. It is selectively cytotoxic for cells with genomic damage, i.e., for tumor cells, both in vitro and in vivo. All cell types exposed to SINE in vitro undergo G1 ± G2 cell cycle arrest, followed by a 'genomic fidelity' review, and cells with significant genomic (DNA) damage are induced to undergo apoptosis. Normal cells, with minimal or no DNA damage, 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.

Preclinical Safety

Sprague-Dawley rats and cynomolgus monkeys were chosen as the toxicology species for the selinexor nonclinical safety program. In both species, the primary effects of oral Selinexor were dose-dependent reductions in food intake and body weight (or reductions in body weight gain), with minimal clinical symptoms (no or mild non-bloody diarrhea), associated primarily with gastrointestinal atrophy. Similar effects are observed in mice and dogs. At high repeated doses of Selinexor associated with marked weight loss, there were changes in cerebellar granular layer neurons in both rats (≥300 mg/m^2) and monkeys (≥72 mg/m^2), but only monkeys showed any CNS symptoms. No central nervous system (CNS)-related adverse side effects were observed in the GLP, rat and monkey 4-cycle toxicity studies. A GLP, rat neurofunctional study (Irwin test) has also been performed at dose levels of 12, 60, or 300 mg/m2 (2, 10, and 50 mg/kg). No behavioral changes were observed at all doses tested.

In the pivotal, GLP, 4-week monkey study, there was no evidence of a direct or indirect effect of Selinexor on the morphology and intervals of the ECG at up to 36 mg/m2 (3 mg/kg). Based on these results, QT prolongation or other cardiac effect does not appear to be a safety concern for Selinexor.

In summary, dose limiting toxicity (DLT)/mortality in both rats and monkeys is related primarily to marked weight loss with atrophy of the gastrointestinal (GI) tract and noncritical effects on other major organs.

Preclinical Efficacy

In vitro experiments with continuous (~72 hour) exposure to Selinexor demonstrated potent pro-apoptotic activity across a broad panel of tumor-derived cell lines and patient samples in culture including multiply-resistant cancers, with the majority of IC50s for cytotoxicity <800 nM and most hematologic tumor lines having IC50s of 20-400 nM for Selinexor. In contrast, normal cells typically underwent (or remained in) cell cycle arrest but were resistant to apoptosis-induction; cytotoxicity IC50s were typically >5 μM. As noted above, Selinexor had little effect on normal (nonmalignant) lymphocytes or other nontransformed cells, which correlated with the low incidence in animals of the typical side effects seen with most anti-cancer therapies such as significant myelosuppression, alopecia, mucositis and other gastrointestinal (GI) dysfunction.

Selinexor and other SINE analogs have been administered in efficacy studies to mice and dogs and in toxicology studies to rats and monkeys. Efficacy was demonstrated in mouse models of myeloma, mantle cell lymphoma (MCL), and T-cell acute lymphocytic leukemia (T-ALL) xenografts. Moreover, efficacy including significant survival advantages was demonstrated in acute myeloid leukemia (AML) [MV4-11 (FLT3-ITD)] (Ranganathan 2012, Etchin 2012) and chronic lymphocytic leukemia (CLL) (TCL-1) leukemografts. Efficacy was also demonstrated in solid tumor xenografts including prostate, breast, liver, glioblastoma, kidney and colon cancers.

3.2 Selinexor: Clinical Summary

A brief summary of key aspects the clinical evaluation of Selinexor is presented below. Further detailed information is provided in the Investigator's Brochure.

Study Designs

Karypoharm Therapeutics, Inc. (subsequently referred to as Karyopharm) is currently conducting three open label Phase 1 clinical trials to assess the safety, tolerability and efficacy of Selinexor given orally 2-3 times per week. The first study (KCP-330-001) is in patients with advanced hematological malignancies, the second (KCP-330-002) is in patients with advanced or metastatic solid tumor malignancies and the third (KCP-330-003), a food effect study, is in patients who have metastatic, locally advanced or locally recurrent soft tissue or bone sarcomas. All patients entering these single-agent phase 1 studies have relapsed after available therapies and have objectively progressing tumors at time of study drug initiation. As of December 15, 2014 550 patients with tumors have been treated with selinexor, and the overall safety profile has not changed. The food effect study was initiated in July 2013, so preliminary safety or efficacy data is not yet available.

KCP-330-001 is a dose escalation study in patients with advanced hematologic malignancies. KCP-330-002 is a dose escalation study in patients with advanced metastatic solid tumors. Dose escalation began at 3mg/m^2 given at 10 doses per cycle (Monday/Wednesday/Friday on weeks 1 and 3; Monday/Wednesday on weeks 2 and 4). The dose limiting toxicities (DLTs) were anorexia/nausea and fatigue at 40mg/m^2 (10 times per 4-week cycle) in KCP-330-002 and the maximum tolerated dose (MTD) was 30mg/m^2. Based on similar adverse events in KCP-330-001, escalation beyond 30mg/m^2 (10 times per cycle) was not performed. The recommended phase 2 dose (RP2D) for 10 times per cycle dosing is 30mg/m^2. Reduced intensity dosing at twice weekly (8 times per cycle, Days 1 & 3 of each week) has shown improved tolerability. Dose escalation on this schedule in KCP-330-002 is ongoing; Dose level 50mg/m^2 cleared DLT. Escalation on this twice-weekly schedule in KCP-330-001 is currently proceeding at 55mg/m^2. In patients with relapsed AML, escalation is currently ongoing at 50mg/m^2 on the twice weekly schedule.

Clinical Evidence of Anti-Cancer Activity

KCP-330-001: A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients with Advanced Hematological Malignancies

This study includes patients with relapsed and refractory hematologic malignancies. KPT-330 is orally administered in escalating dose levels at 10 doses/cycle (Schedules 1and 2) or 8 doses/cycle (Schedule 3) as follows:

- Schedules 1 and 2: selinexor is administrated PO 3 times a week every other day for weeks 1 and 3 (QoDx3/wk). For weeks 2 and 4, drug is dosed on days 1 and 3 of each week (BIW). One cycle is 28 days or 10 doses. At doses > 12mg/m2, a “run in” week at 12 mg/m2 QoDx3/wk precedes Cycle 1 (10 doses per 4 weeks); this 10-dose regimen with the run-in week is designated Schedule 2.

- Schedule 3: selinexor is administrated PO on days 1 and 3 of each week (BIW). One cycle is 28 days or 8 doses.

There are three Arms to this study: Arm 1 includes patients with the relatively indolent hematologic malignancies multiple myeloma (MM), Waldenström’s Macroglobulinemia (WM), Non-Hodgkin’s Lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Arm 2 includes patients with acute myeloid leukemia (AML). Because of the rapidly progressive nature of AML, Arm 2 began dosing at 16.8mg/m2 after dose limiting toxicity (DLT) clearance in cohort 3 (12 mg/m2) and initiation of

16.8mg/m2 dosing in Arm 1, i.e., in the indolent hematologic malignancy patients. Arm 3 includes up to 12 patients with refractory PTCL or CTCL treated at a dose of 30mg/m2 on Schedule 3. No patients have been enrolled in this Arm to date. All patients entered study with documented disease progression having relapsed following all proven and many experimental therapies. Intrapatient dose escalation is permitted once patients have cleared the next higher dose cohort.

Arm 1: As of 01-July-2013, a total of 38 patients on Arm 1 (17 MM, 2 WM, 15 NHL and 4 CLL) have been enrolled at doses ranging from 3 to 30 mg/m2 on Schedule 1 and 2 (10 doses/cycle). As of 01-July-2013, 3 patients have been enrolled at 35 mg/m2 on Schedule 3. The maximum tolerated dose (MTD) has not yet been reached in this Arm, and as of 11/11/13 (personal communication with John McCartney, Karyopharm) dose level 40mg/m^2 had not produced DLT and dosing is proceeding at 55mg/m^2 on schedule 3 (BIW dosing).

Arm 2: As of 01-July-2013, a total of 27 patients on Arm 2 (AML) have been enrolled, all refractory to standard therapy (median number of prior therapies = 2; range 1-7), including hypomethylating agents, and treated at doses ranging from 16.8 mg/m2 to 30 mg/m2 on Schedule 2 (13 doses/cycle) and at a dose of 30 mg/m2 on Schedule 3. Three patients achieved a complete response (CR) without hematologic recovery and one patient achieved CR with recovery of ANC and platelets. No DLTs were observed in these cohorts and MTD has not yet been reached. As of 01-July-2013, no clinically significant cumulative drug toxicities have been observed in either Arm1 or Arm 2, with 5 patients on study for >6 months. Currently, dosing is proceeding at 50 mg/m^2 on schedule 3 (BIW dosing).

Arm 3: One patient has been enrolled on Arm 3 to date.

KCP-330-002: A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients with Advanced or Metastatic Solid Tumor Malignancies

This study includes patients with advanced, refractory solid tumors. Selinexor) is orally administered in escalating dose levels at 10 or 13 doses/cycle (Schedules 1 and 2) or 8 doses/cycle (Schedule 3) as described above for study KCP-330-001.

As of 01-July-2013 68 patients received selinexor across 7 dose levels (3 to 40 mg/m2) on Schedule 1 and two dose levels in Schedule 2 (35 and 40 mg/m2). Dosing at 50 mg/m^2 on Schedule 3 (BIW) was completed without DLT as of 11/11/13 (11/11/13 personal communication with John McCartney, Karyopharm).

No DLTs were observed in the initial six cohorts at doses ranging from 3 to 30 mg/m2 on Schedule 1/2. Two DLTs were observed out of 3 patients at 40 mg/m2: one was Grade 3 anorexia with dehydration and fatigue, the other was Grade 3 fatigue with Grade 1-2 anorexia. Although neither of these patients with DLTs received optimal supportive care/medications (such as anti nausea, appetite stimulators and glucocorticoids), given the entire clinical picture, the decision was made to declare 30 mg/m2 the MTD for solid tumor patients treated on Schedules 1/2, and both of these patients with DLTs had their doses reduced from 40 mg/m2 to 30 mg/m2. A third patient treated at 40 mg/m2 on Schedule 2 tolerated therapy well, but given the other patients, her dose was reduced

to 30mg/m2 as well. Twelve (12) additional patients were enrolled at this dose as part of the expansion phase on Schedule 2.

Six patients were treated at 35 mg/m2 on Schedule 3. One DLT of Grade 3 nausea/vomiting, with fatigue was observed in patient (043-101) with melanoma who had concomitant C. difficile infection; this patient also had a partial response on CT scan after 2 cycles but the patient withdrew consent. Three patients have cleared DLT assessment in cycle 1 at 40 mg/m2 on Schedule 3 (July 25, 2013), and dose escalation to 50 mg/m2 is has opened. Based on the data to date, the Phase 2 recommended starting dose was determined as 35 mg/m2 on Schedule 3 and 18 patients were enrolled to the study as part of the expansion phase on Schedule 3. Patients who tolerate 35 mg/m2 on Schedule 3 may have their doses escalated to 40 mg/m2 if requested by their treating physician. Interim KCP-330-002 study results were presented at the 2013 ASCO annual meeting (Razak, 2013).

Preliminary evidence of clinical activity was appreciated in study KCP-330-002. One patient (043-805) with K-ras mutant colorectal cancer (CRC) treated with all approved agents (except regorafenib) showed a partial response (PR) by RECIST 1.1 criteria after 4 cycles of therapy. Several other patients with heavily pretreated CRC have also shown reduction in tumor mass, CEA levels, and/or ascites, on study for >4 months (043-001, 043-014, 043-016). Patients with cervical cancer have shown stable disease for ≥6 months (043-002, 043-007). Two patients with squamous cell cancers of the head and neck region have shown stable disease (043-804, 043-013).

Phase 1 safety data for selinexor

For the two ongoing clinical trials (KCP-330-001 and KCP-330-002), a total of 97 patients comprise the safety population as of the 31 May 2013 data cut-off (over 130 patients have been dosed to date, but the data sets reported here are through 31 May 2013).

KCP-330-001: A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients with Advanced Hematological Malignancies

The AEs for AML patients (Arm 2) in this study are summarized in the table below.

KCP-330-001 (AML cohort, n = 16): Toxicities attributed to selinexor

Adverse Event	Grade 1	2	3	4	Total
Cardiovascular					
Hypotension	1 (6%)		1 (6%)		2 (13%)
Gastroenterological					
Anorexia	2 (13%)	5 (31%)			7 (44%)
Weight loss	5 (31%)				5 (31%)
Diarrhea	1 (6%)	1 (6%)			2 (13%)
Nausea	6 (38%)	2 (13%)	1 (6%)		9 (56%)
Vomiting	5 (31%)				5 (31%)
Heme					
Neutrophil count decreased				1 (6%)	1 (6%)
Platelet count decreased				2 (13%)	2 (13%)
Lab abnormalities					
Aspartate aminotransferase increased	1 (6%)		1 (6%)		2 (13%)
Hypokalemia			1 (6%)		1 (6%)
Hyponatremia	2 (13%)				2 (13%)
Neurology					
Headache			2 (13%)		2 (13%)
Ophthalmology					
Blurred vision	3 (19%)				3 (19%)
Systemic					
Fatigue	1 (6%)	5 (31%)	2 (13%)		8 (50%)

AE occurring in ≥ 25% of patients

*AEs were counted for each patient once as the highest grade AE experienced

Patients entering this study have heavily pretreated hematologic malignancies. The most common AEs, which are also observed in patients with advanced metastatic solid tumors, are gastrointestinal (GI) in nature. These are Grade 1-2 events are generally responsive to standard supportive care measures. Diarrhea is observed in some patients though relationship to study drug is unclear. Dysgeusia is primarily reported as a metallic taste. Thrombocytopenia is seen, but no bleeding events have been observed, and several patients with Grade 4 thrombocytopenia have remained on therapy for months with intermitted glucocorticoids and/or infrequent transfusions, and good disease control. Severe neutropenia has been relatively uncommon and there is only one case of possibly related febrile neutropenia to date.

Blurry vision has been reported on this and the accompanying study KCP-330-002. The etiology of the blurry vision is not known, and no objective ophthalmological correlates have been observed. Dehydration leading to changes in the refractive index in the lens may be involved. Two of these cases have responded to changes in lens prescription, and all of the cases have resolved or are improving. Nearly all patients entering the study have baseline ophthalmological abnormalities. No drug-related neuroophthalmalogic abnormalities or CNS adverse events have been reported to date.

Increases in liver function transaminases were reported in 3 patients (040-106 Grade 3 AST and ALT elevation, 040-007 Grade 1 ALT elevation, 040-109 Grade 1 AST elevation) without sequelae or total bilirubin elevations; relationship to study drug remains questionable. Patient 040-106's increases rapidly resolved and no AST or ALT changes occurred on retreatment with the drug at the same dose for 5 additional doses; this patient then left the study due to progressive AML. Nonclinical toxicology studies showed no laboratory or pathological evidence of liver toxicity. Cumulative toxicities have not been significant to date, but data at this point are limited. No drug-associated deaths have been reported on study as of 01 July 2013.

KCP-330-002: A Phase I Study of the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of the Selective Inhibitor of Nuclear Export (SINE) KPT-330 in Patients with Advanced or Metastatic Solid Tumor Malignancies

The patients (N=50) compromising the current safety population were treated at escalated protocol doses of 3-40 mg/m2 on Schedule 1 or 2 and at 35-40 mg/m2 on Schedule 3. A summary of the reported related treatment-emergent adverse events that were considered at least possibly related to drug administration occurring in ≥2 patients is displayed in Table 14, pages 82-83 in the IB and in the table below. The most common AEs are GI in nature, typically grade1-2 anorexia, nausea and vomiting, which are generally responsive to standard supportive care measures.

Diarrhea is observed in some patients though relationship to study drug is unclear. Dysgeusia is primarily reported as a metallic taste. Systemic AEs are primarily related to fatigue. Myelosuppression has generally been manageable. Platelet counts appear to be the most sensitive to treatment with selinexor, similar to (though less common) that observed on the hematologic cancer study KCP-330-001. Asymptomatic hyponatremia Grade 3 has been reported in 8 patients. Increases in liver function transaminases were reported in 3 patients.

Ocular symptoms of various kinds have been reported by a number of patients. The most common is blurred vision. None of the ocular symptoms have been progressive, none have lead to therapy discontinuation, and professional ophthalmological examinations, instituted per protocol based on early reports, have disclosed no common findings. Many of the patients entering the study have unrecognized ophthalmological disorders that are discovered during these examinations.

It should be noted that no reports of major organ dysfunction have occurred to date including in the patients with DLT. In particular, there has been no clinically significant renal, liver, pancreatic, cardiac or pulmonary dysfunction. No drug-associated deaths have been reported on study as of 01 July 2013. Moreover, there have been no reports of central or peripheral neurological toxicities. Therefore, the primary side effects of selinexor in doses up to 40 mg/m^2 on Schedules 1 (10 doses per cycle) and up to 50 mg/m^2 3 on schedule 3 (BIW or 8 doses per cycle) are reversible anorexia, weight loss and fatigue which responds to aggressive supportive care measures. These side effects have been considerably more prominent in weeks 1 and 3 when patients receive 3 doses (M/W/F) as compared with weeks 2 and 4 when patients receive 2 doses only (M/W). These observations have led to the current amendment for twice weekly dosing schedule in planned phase 2 trials.

In summary, the primary AEs associated with selinexor in patients with advanced solid tumor malignancies are GI in nature and respond to aggressive standard supportive care measures. Institution of prophylactic supportive medications and dietary counseling can greatly reduce or eliminate much of the anorexia, nausea, or weight loss associated with selinexor and permit long term dosin

KCP-330-002: Toxicity attributed to selinexor

Adverse Event	Grade				Total
	1	2	3	4	
Cardiovascular					
Hypotension			1 (2%)		1 (2%)
Dermatology					
Alopecia	1 (2%)				2 (4%)
Periorbital edema	1 (2%)	1 (2%)			2 (4%)
Endocrinology					
Flushing	3 (6%)				3 (6%)
Gastroenterology					
Anorexia	10 (20%)	21 (42%)	3 (6%)		34 (68%)
Weight loss	11 (22%)	10 (20%)			21 (42%)
Abdominal pain	3 (6%)				3 (6%)
Constipation	3 (6%)	1 (2%)			4 (8%)
Diarrhea	11 (22%)	3 (6%)			14 (28%)
Dry mouth	8 (16%)	1 (2%)			9 (18%)
Dysgeusia	16 (32%)	8 (16%)			24 (48%)
Dyspepsia	4 (8%)	1 (2%)			5 (10%)
Nausea	21 (42%)	14 (28%)	4 (8%)		39 (78%)
Vomiting	17 (34%)	9 (18%)	3 (6%)		29 (58%)
Hematologic					
Anemia	1 (2%)	10 (20%)	3 (6%)		14 (28%)
Neutrophil count decreased			1 (2%)		1 (2%)
Platelet count decreased	3 (6%)	2 (4%)	2 (4%)	3 (6%)	10 (20%)
White blood cell decreased		1 (2%)	1 (2%)		2 (4%)
Lab abnormalities					
Alanine aminotransferase increased	2 (4%)		1 (2%)		3 (6%)
Aspartate aminotransferase increased	1 (2%)	1 (2%)			2 (4%)
Creatinine increased	2 (4%)				2 (4%)
Dehydration	1 (2%)	1 (2%)	2 (4%)		4 (8%)
Hypokalemia	1 (2%)	1 (2%)			2 (4%)
Hypomagnesemia	1 (2%)	1 (2%)			2 (4%)

KCP-330-002: Toxicity attributed to selinexor (continued)

Adverse Event	Grade 1	2	3	4	Total
Hyponatremia	1 (2%)		8 (16%)		9 (18%)
Musculoskeletal and connective tissue					
Generalized muscle weakness	2 (4%)				2 (4%)
Neurology					
Dizziness	4 (8%)	1 (2%)			5 (10%)
Headache	3 (6%)				3 (6%)
Paresthesia	2 (4%)				2 (4%)
Ophthalmology					
Blurred vision	5 (10%)	2 (4%)			7 (14%)
Dry eye	2 (4%)				2 (4%)
Flashing lights	3 (6%)				3 (6%)
Floaters	3 (6%)				3 (6%)
Pulmonary					
Dyspnea	1 (2%)	1 (2%)			2 (4%)
Systemic					
Fatigue	4 (8%)	23 (46%)	8 (16%)		35 (70%)
Malaise		2 (4%)			2 (4%)

AE occurring in ≥ 25% of patients

*AEs were counted for each patient once as the highest grade AE experienced

Clinical Pharmacokinetics

Detailed pharmacokinetic (PK) and pharmacodynamic (PDn) analyses and serial tumor biopsies were performed in both studies and suggested a fairly proportional increase in Cmax and AUC with increasing dose, with no accumulation and without affecting half-life or clearance of Selinexor. At 30 mg/m^2, $AUC_{0\text{-last}}$ (4375 ng*h/mL) was comparable to the anti-tumor exposure observed in mice and dogs. T_{max} (~3 h) and $T_{1/2}$ (6-7 h) were consistent across doses. Significant increase (2-20x) in XPO1 messenger ribonucleic acid (mRNA) levels (PDn marker) in circulating leukocytes was observed at all doses, with higher doses demonstrating higher levels of XPO1 mRNA induction. Analysis of tumor biopsies confirmed nuclear localization of TSPs (*e.g.*, p53, FOXO3A, IκB) and apoptosis of cancer cells following selinexor administration.

3.3 Rationale for use of Selinexor in Hematologic Malignancies

Pre-clinical studies have demonstrated striking anti-leukemic activity in acute lymphoblastic leukemia and acute myelogenous leukemia for selinexor and similar, earlier compounds (Etchin, 2013) with little effect on normal hematopoetic cells or myelosuppression. In an ongoing phase 1 study, the dose of selinexor was escalated starting at 3 mg/m^2 in patients with solid tumors, multiple myeloma, lymphoma, and leukemia. Activity has been noted in a variety of malignancies, including multiple myeloma, lymphoma, and leukemia.

Therapy-related MDS/AML and poor risk *de novo* MDS/AML is characterized by an increased frequency of lost or mutated p53 (20-30% as we have shown in therapy-related MDS/AML and 5-10% in *de novo* MDS/AML)(Shih, 2013). We have also noted that both p53 alleles may be mutated

and/or lost, but in this situation, the related TSP p73 can be engaged (Mass 2011). XPO1 blockade forces p53 and p73 nuclear retention and, even in cells harboring only one p53wt allele, activates its downstream cell cycle regulatory and apoptotic functions (Turner 2012). However, upregulated XPO1 can also promote p53 “mislocalization” and dysfunction in cancer cells even in the absence of mutation or allele loss.

NFkB is also an important pathway in MDS/AML. The NFkB pathway is activated in MDS/AML as it is in other malignancies, as a means to enhance proliferation. Inhibition of NFkB by the proteosome inhibitor bortezomib has shown activity in multiple myeloma, and it’s use is being explored in AML (and MDS). We and others have shown that inhibition of NFkB leads to apoptosis in MDS/AML using sodium salicylate (Disalcid) (Klampfer, 1999). Upregulation of NFkB is associated with chemotherapy resistance in AML (and MDS) due to either constitutive activation or chemotherapy-induced upregulation, Therefore, inhibition of NFkB may be effective, particularly for MDS or AML which can have constitutive or induced (during chemotherapy administration) NFkB upregulation, thereby promoting resistance to chemotherapy. Blockade of XPO1 prevents export of I-κp from the nucleus, and was shown to induce long term inhibition of NF-κB activity (Gupta 2010) and therefore Selinexor may induce apoptosis in MDS or AML, and/or may sensitize MDS/AML to standard chemotherapy.

The Wnt signaling pathway plays a role in the maintenance of hematopoetic stem cells. Upregulated Wnt signaling results in accumulation of nuclear non-phosphorylated beta catenenin, leading to activation of MYC and CCND1 and is therefore known to be oncogenic. Nuclear non-phosphorylated beta catenin was seen in 18/44 (41%) of MDS BM biopsies and was associated with higher IPSS risk disease, -7/del(7q) (poor risk) karyotypes, and poor clinical outcomes (Xu, 2010). The effects of interrupted XPO1 activity on APC and nuclear beta catenin levels is unclear, especially since beta catenin can also undergo nuclear-cytoplasmic shuttling independent of APC and XPO1. However, Selienexor treatment was shown to reduce MYC levels in myeloma and HCC cells.

Other clients for XPO1 which may be more relevant for AML include FOXO3 and NPM1 as discussed in section 1.1.2. The effects of selinexor on these TSPs are being evaluated in an ongoing study of selinexor in AML.

Further information about the preclinical pharmacology and toxicology of selinexor is presented in the Investigator’s Brochure.

3.4. Rationale for dose and schedule

In general, selinexor has been well tolerated across in patients with advanced cancer. Drug related grade 1-2 nausea, grade 1-2 vomiting (intermittent, rapidly responding to anti-emetics or self-resolving), grade 1-2 fatigue, grade 1 or 2 dysgeusia, grade 1-2 anorexia, grade 1 weight loss have been observed. These side effects have been considerably more prominent in weeks 1 and 3 when patients receive 3 doses (M/W/F) as compared with weeks 2 and 4 when patients receive 2 doses only (M/W).

Based on the observed better tolerability in the twice weekly dosing compared with 3X/week dosing, an alternative twice weekly schedule consisting of 8 doses / 4 week cycle was explored (referred to as “Schedule 3”).

In the solid tumor phase 1 study, six patients were treated at 35 mg/m^2 on Schedule 3. One DLT of Grade 3 nausea/ vomiting, with fatigue was observed in patient (043-101) with melanoma who had concomitant C. difficile infection; this patient also had a partial response on CT scan after 2 cycles but the patient withdrew consent. Three patients have cleared DLT assessment in cycle 1 at 40 mg/m^2 on Schedule 3 (July 25, 2013), and more recently, dose escalation to 50 mg/m^2 has not resulted in dose limiting toxicity. .Based on the data to date, the Phase 2 recommended starting dose was determined as 35 mg/m^2 on Schedule 3 and 18 patients were enrolled to the study as part of the expansion phase on Schedule 3.

In the phase 1 hematologic malignancies study, as of 01-July-2013, patients were enrolled at doses of up to 40 mg/m^2 on Schedule 3 without DLT and dosing is currently proceeding at 55 mg/m^2 (indolent hematologic malignancies arm) without DLT. In the AML arm, MTD was not reached as of July 2013 at a dose of 30 mg/m^2 and 4 CRs were seen in AML patients at doses below 35 mg/m^2 BIW (CRs seen at doses of 16.8-23 mg/m^2 on TIW alternating with BIW schedule). Dosing for the AML arm (Arm 2) is currently proceeding at 50 mg/m^2.

It should be noted that no reports of major organ dysfunction have occurred to date, including in the patients with DLT. In particular, there has been no clinically significant renal, liver, pancreatic, cardiac or pulmonary dysfunction. Moreover, there have been no reports of central or peripheral neurological toxicities. Therefore, the primary side effects of selinexor in doses up to 40 mg/m^2 on Schedules 1 (10 doses per cycle) and up to 50 mg/m^2 3 (8 doses per cycle) are reversible anorexia, weight loss and fatigue.

Data from phase I studies of selinexor indicate that prophylactic antiemetic and anti-anorexia therapy imporves the tolerance of selinexor. As a result, all patients will take two prophylactic medications during cycle 1 of Selinexor, and these medications may be tapered or discontinued during cycle 2 or later in treatment. See section 9.1.3 for details.

Given the improved tolerability of twice weekly dosing compared to three times per week dosing, and the activity in hematologic malignancies at and below 70 mg/m^2 per week, selinexor for 8 doses in a 4 week cycle (i.e., 280mg/m^2 in 4 weeks) was the initial starting schedule for this study. Impaired tolerance, due primarily to fatigue, was noted in the first two patients enrolled on this study, which is the first selinexor study in the MDS population. This impaired tolerance may be due to the advanced age of MDS patients combined with the anemia related to the MDS. Therefore, the dosing schedule was adjusted to provide a dosing break. Selinexor will be dosed twice per week for two weeks followed by 1 week of no therapy.

Recent analysis of the existing PK data from Phase 1 trials KCP-330-001 and KCP-330-002 supports the use of fixed rather than BSA-based dosing. The 5th and 95th percentile for BSA values encountered to date in Phase 1 trials KCP-330-001 and KCP-330-002 are 1.5 and 2.3 m^2, respectively (N=331). PK values (C_{max} and $AUC^{(0-\infty)}$) for a given flat (fixed) dose of selinexor were similar across this typical BSA range, indicating that exposure is not strongly correlated with BSA. Basedo n the analysis of this PK data, the recommended starting dose will be changed to a flat dose of 60mg (~35mg/m^2)

3.5. Study Rationale: Summary

Preclinical *in vitro* and *in vivo* data and phase 1 clinical data have shown that both hematologic and solid tumor cells are susceptible to single-agent cytotoxicity by selinexor, consistent with its restoration of multiple tumor suppressor gene functions and growth regulatory pathways leading to the death of cancer cells. The ongoing phase 1 study has demonstrated the safety of the proposed phase 2 dose (35 mg/m^2) and activity in hematologic malignancies including MM, NHL and CLL. In a separate arm of the Phase 1 study heavily pretreated elderely AML patients were treated with selinexor at doses of 16.8 mg/m^2 to 40 mg/m^2. Three patients achieved CR (2 with complete hematological recovery and one bone marrow CR without hemetologic recovery) and several patients had stable diease. Given the novel mechanism of action, the rationale for XPO1 inhibition by selinexor in AML/MDS, and the phase 1 safety and efficacy data, the risk benefit assessment favors further development of selinexor in hematologic malignancies, including MDS.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a phase 2, single arm, open-label study designed to assess the activity of selinexor in patients with myelodysplastic syndromes who have progressed on or have not responded to an adequate trial of hypomethylating agents.

4.3 Objectives

Primary Objective:

- To evaluate the efficacy (overall response rate: CR+marrow CR + PR + HI) of Selinexor in patients with myelodysplastic syndromes

SecondaryObjectives:

- To determine response duration in patients with MDS who achieve a response of stable disease, HI, mCR, PR, CR.
- To describe the frequency of Stable Disease
- To describe survival of MDS patients receiving selinexor after study enrollment
- To assess the response rate and response duration in therapy-related MDS
- To assess tolerability of chronic Selinexor therapy in patients with Myelodysplastic Syndromes.
- To study the pharmacodynamics (PDn) of Selinexor.

4.4 Intervention

4.3.1. Rationale for the Study Design

Various pathways which are aberrantly suppressed or activated in myeloid malignancies are modulated by the nuclear retention or export of transcriptional regulatory elements via XPO1. These pathways modulate the growth of myeloid malignancie and/or contribute to resistance to therapy (eg., NF-kβ). In *in vitro* studies, selinexor induces apoptosis in leukemia cell lines and in primary (patient-derived) AML cultures, which is correlated to nuclear retention of tumor suppressors which

are thought to have a role in the pathobiology of MDS. The goal of this study is to determine if selinexor can induce responses in this population, for whom best supportive care is the standard treatment option, and median survival is 4-6 months.

4.3.2. Study Design

Selinexor will be taken twice per week for 2 weeks, followed by 1 week of no therapy. Disease assessments will be performed after cycle 1 and 2, then every other month therafter until CR or maximal response is achieved, at time of disease progression or when clinically indicated, using the Modified MDS International Working Group response criteria. Treatment will be allowed indefinitely, barring disease progression, excessive toxicity, or withdrawal of consent. Pharmacodynamic studies will be performed at baseline, cycle 1 day 14 (for first 10 patients), after cycle 1, 2, and 4 to assess the biological activity of Selinexor. A total of 20 adult patients with myelodysplastic syndromes will be enrolled into this study. After treatment is stopped, patients will be followed indefinitely every three months for survival. The study will be conducted at Memorial Sloan-Ketteriing Cancer Center.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Product: Selinexor (KPT-330)

Classification: Cell biological modifier: Apoptosis-inducing agent

Mechanism of action: Selinexor is a Selective Inhibitor of Nuclear Export (SINE) that specifically blocks nuclear export by slowly-reversible covalent binding to XPO1 (also called CRM1) protein.

5.1. Formulation

Tablets for selinexor oral administration will be supplied in two (2) strengths: 10 and 25 mg of active ingredient per tablet, or 20mg tablets (supplied in blister packs). The initial drug product for the study will be the 10 and 25 mg tablets, with transition to the 20mg tablets as these supplies become available. Bulk bottles of 50 tablets per bottle will be supplied for each of the two strengths. The tablets are clear coated with Opadry II clear and prepared from a common blend prepared from a wet granulation of active compound (SELINEXOR), Kollidon® 30 (polyvinyl pyrrolidone), sodium lauryl sulfate, croscarmellose sodium, and Avicel PH-101 (Microcrystalline cellulose). The granulation is adjusted to final compression blend with Avicel PH-102 (Microcrystalline cellulose), Aerosil® (colloidal silicon dioxide), magnesium stearate, and additional croscarmellose sodium. All tablet excipients are GRAS and suitable for use in pharmaceuticals.

5.2. Labelling

Each bottle of selinexor tablets will be labelled in accordance with current ICH GCP, FDA and specific national requirements.

5.3. Storage

10 and 25 mg Tablets on Bottles

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. 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).

20 mg Tablets in Blister Packs

- Selinexor tablets (20 mg) are currently in ongoing stability studies. The expiry will be based on concurrent stability studies and extended during the course of the study as further stability data becomes available.
- All selinexor tablets must be kept in an appropriate, limited access, secure place until dispensed, destroyed or returned to Karyopharm Therapeutics, Inc. or designee for destruction.
- Selinexor tablets can be stored at room temperature or refrigerated, at or below 86 ˚F or 30 ˚C, do not freeze. Room temperature storage is recommended. The study site will be required to maintain a log of the temperature where the study medication is stored.

5.4. Selinexor Dosing Information

After the initial screening visit and registration in the study, patients will receive selinexor twice weekly orally at a starting dose of 60mg. The dosing schedule is two doses per week for 2 weeks, followed by 1 week of no therapy. Dose reductions are permitted as described in section 9.2. In addition, patients will receive anorexia and nausea prophylactic medications prior to their first dose (detailed in section 9.1.3).

Selinexor is to be taken with solid food consumption together with 240 mL (8 ounces) of water.

5.5. Drug Product Accountability

Study drug for the study are provided by the Karyopharm and will be labelled as per the applicable regulations. Sites must request study drug by submitting an order form directly to the drug depot in order for the study drug to be shipped to the site pharmacy. 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 institutional study monitor during each monitoring visit and at the close out visit.

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).

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 clinical drug supplies must be kept in an appropriate, limited access, secure place until used or returned to Karyopharm 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.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY.

6.2 Subject Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Written informed consent in accordance with federal, local, and institutional guidelines
2. Age ≥18 years
3. Patients with Myelodysplastic Syndromes refractory (primary or acquired resistance) to hypomethylating agents. At least 4 1-month cycles of prior decitabine or SGI-110 OR 6 1-month cycles of 5-azacytidine (IV, subcutaneous, or oral) is required unless the patient has progressive disease prior to completing the required number of cycles.
4. Histologically confirmed diagnosis of a Myelodysplastic Syndrome, meeting criteria for any subtype in the FAB or WHO classification systems with any IPSS score.
5. Patients with MDS who relapse after allogeneic stem cell transplant are eligible if they received standard dose decitabine or 5-azacytidine prior to or after stem cell transplant as defined in inclusion criteria 3.
6. If patient has undergone prior allogeneic stem cell transplant, they must be greater than 100 days post transplant and have ≤ grade 2 graft-versus-host disease.
7. There is no upper limit on the number of prior treatments provided all inclusion/exclusion criteria are met.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 (Appendix 1).
9. Patients receiving erythropoietin (darbepoetin, epoetin alfa) must be on a stable dose and with stable transfusion requirement or hemoglobin level during the 8 weeks prior to study entry.
10. Adequate hepatic function within 21 days prior to C1D1: total bilirubin <2 times the upper limit of normal (ULN), asparate aminotransferase (AST) <2.5 times ULN and alanine aminotransferase (ALT) <2.5 times ULN.
11. Adequate renal function within 21 days prior to C1D1: estimated creatinine clearance of ≥ 30 mL/min, calculated using the formula of Cockroft and Gault.
12. 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

6.3 Subject Exclusion Criteria

1. Patients who are pregnant or lactating;
2. Chemotherapy or immunotherapy or any other anticancer therapy ≤3 weeks prior to cycle 1 day 1. Hydroxyurea may be continued until 72 hours prior to first dose and at least 24 hours before the baseline bone marrow aspiration is performed;
3. Major surgery within four weeks before Day 1;
4. Unstable cardiovascular function defined as symptomatic ischemia, uncontrolled clinically significant conduction abnormalities (ie: ventricular tachycardia on antiarrhythmics are excluded and 1st degree AV block or asymptomatic LAFB/RBBB will not be excluded), congestive heart failure (CHF) of NYHA Class ≥3, or myocardial infarction (MI) within 3 months;
5. Uncontrolled active infection requiring systemic antibiotics, antivirals, or antifungals within one week prior to first dose; Prophylactic antimicrobials are permitted.
6. Known to be HIV seropositive;
7. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface *antigen*);
8. Patients with another *active* malignancy. Asymptomatic sites of disease are not considered active. Treated or untreated sites of disease may be considered inactive if they are stable for at least 2 months and are not expected to require therapy for 4 months.
9. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea.
10. Grade ≥2 peripheral neuropathy at baseline (within 21 days prior to cycle 1 day 1).
11. History of seizures, movement disorders or cerebrovascular accident within the past 1 years prior to cycle 1 day 1.
12. Patients with macular degeneration with markedly decreased visual acuity, patients with markedly decreased visual acuity (no specific etiology) or uncontrolled glaucoma.
13. Patients who are significantly below their ideal body weight (BMI < 17)..
14. Serious psychiatric or medical conditions that could interfere with treatment.

7.0 RECRUITMENT PLAN

Both men and women and members of all races and ethnic groups are eligible for this trial. Potential candidates for this study will be discussed during the weekly Leukemia Service new patient conference. In addition, potential study participants will be identified by a member of the patient's treatment team, the principal investigator, or research team. If the investigator is a member of the treatment team he or she will screen their patient's medical records and discuss the study with the patient. Potential study candidates identified during clinic visits or in clinical care meetings on other

services, such as the Stem Cell Transplant Service, will be referred to the principal investigator for screening and clinical management while on the study.

8.1 PRETREATMENT EVALUATION

The investigator must not start any study related procedure before informed consent form is signed and dated by the patient (and impartial witness, if applicable), and investigator. The investigator is obliged to give the patient thorough information about the study and study related assessments, and the patient should be given ample time to consider his or her participation. If the screening physical exam (including vital signs, oxygen saturation) is done within five days of starting the study treatment, the exam does not need to be repeated to initiate treatment.

Within 30 days of starting treatment:

- Sign written informed consent

Within 21 days of starting treatment:

- Medical history and review of prior cancer treatment
- Review of concomitant medications
- Complete physical exam including oxygen, routine clinical neurologic examination, and visual acuity examination
- 12-lead electrocardiogram (baseline assessment)
- Routine urinalysis and microscopic exam if indicated (baseline assessment)
- Comprehensive metabolic panel, uric acid, thyroid stimulating hormone (TSH)
- Coagulation panel (PT, INR, aPTT)
- Serum pregnancy test
- Chest radiograph (baseline – for subsequent comparison. If CT chest or chest X-ray done within 30-days prior to start of treatment, no chest X-ray is required)
- Opthalmalogy exam
- Bone marrow biopsy and aspirate (for baseline disease assessment and for research sample procurement)
- Baseline blood samples for exploratory pharmacodynamics assessments

9.0 TREATMENT/INTERVENTION PLAN

9.1. Treatment Plan

9.1.1. Treatment Dose and Schedule

The starting dose of selinexor will be 60mg (PO) 2 times a week (+/- 1 day) with at least 36 hours between doses. Selinexor will be given for 2 weeks, followed by 1 week of no therapy. The scheduled dosing days should be the same days in each week. One cycle is 21 days or 4 doses (plus 1 week off). The drug administration days will occur on the same days within a cycle (ie Tue/Thu) but may be adjusted as needed from cycle to cyle. Dosing is not required to start on Day

#1 of a given cycle, which will coincide with the patient's clinic visit. Depending on patient preference for dosing days, and given the need to have results from day #1 laboratory evaluations, dosing can begin on days 1, 2, or 3 of a given cycle, but preferentially with consistency from one cycle to next.

Patients will be required to keep a drug dosing diary and symptom diary. Doses should be taken at roughly the same time of day (morning, afternoon, or evening hours), ensuring there is at least 36 hours between doses. Selinexor is taken with solid food consumption. Food should contain at least moderate fat content. Selinexor tablets should not be opened, chewed, or crushed.

Compliance to study medication will be ascertained by use of patient diaries. The date, time and number of tablets consumed 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 medical record 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.

Dose reductions are allowed as decribed in section 9.2 (Table 1).

Patients who come off study after starting study drug because of toxicity, death, or withdrawal of consent prior to undergoing a response assessment will not be replaced and will be considered a treatment failure. Patients who enroll on study but do not receive study therapy will be replaced.

9.1.2. Treatment Duration

Patients may continue on study indefinitely if they are experiencing clinical benefit, barring progression of disease, excessive toxicity,or withdrawal of consent. After discontinuation from treatment, patients will be followed by the study staff for survival status approximately evert three months.

9.2 Dosing Adjustments

Toxicity will be graded according to NCI CTCAE, version 4.03; the therapy modifications described below are applied according to this severity grading.

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

Re-escalation of the study drug is allowed as outlined in the sections that apply for the specific toxicity. If drug-related toxicity requires a treatment delay of more than 21 days the patient is taken off protocol treatment.

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

Based on observations from the ongoing Phase 1 studies in patients with advanced hematological and solid tumors, we note that selinexor shows a reasonably wide therapeutic range, with activities from ~10mg/m2 to ≥50mg/m2. 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.

9.2.1. Dose Modifications for Non-hematologic Toxicity Unrelated to Selinexor

For all ≥ Grade 3 non-hematologic toxicitiies that are NOT selinexor related:

- Hold selinexor dose until AEs resolves to ≤ Grade 1 or baseline (maximum 28 days). Exceptions to this include: Patients with grade ≥3 nausea, vomiting or diarrhea can continue selinexor unless optimal supportive therapies have already been administered for at least 3 days days without improvement of the nausea, vomiting, or diarrhea. Optimal supportive therapies (see Supportive Care Guidelines, Section 9.1.3).
- If the AEs resolve to ≤ Grade 1 or baseline within 28 days, restart Selinexor at the **same** dose.
- If the AEs do not resolve to ≤ Grade 1 or baseline within 28 days of discontinuation of study drug, study drug will be discontinued permanently.

In exceptional situations, if the patient has experienced objective evidence of clinical benefit, and in the opinion of the investigator no safety concerns are present and it is in the best interest of the patient to remain on study, the patient may continue to receive study treatment after the 28-day delay. The rationale for continuing study treatment will be documented in the patient's medical record.

9.2.2. Dose Modifications for Hematologic and Non-hematologic Toxicities Related to Selinexor

The criteria for dose modification for toxicities at least possibly related to selinexor are outlined below in Table 1. Supportive care guidelines for management of selinexor-related toxicities and indications for dose modifications are described in Table 2.

Table 1. Pre-specified Dose Modifications for AEs Related to Study Drug

	Dose Level		
Starting Dose	1	60mg	twice weekly
Dose Reductions	-1	40 mg	twice weekly
	-2	40 mg	once weekly

Table 2. Supportive Care and Dose Modification Guidelines

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Fatigue (common)		
Grade 1	Rule out other causes of fatigue. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor. Insure adequate caloric intake and assess volume status.	Maintain dose.
Grade 2	Rule out other causes of fatigue. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor. Insure adequate caloric intake and assess volume status. For additional support see NCCN fatigue guidelines.	Maintain dose. Consult medical monitor for additional option such as temporarydose reduction or short dose interruptions.
Grade 3	See above 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 one dose level lower
Anorexia or Weight loss		
Grade 1	Rule out other causes of anorexia. Assess dietaryoptions (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor dosing.	Maintain dose.
Grade 2	Rule out other causes of anorexia. Assess dietaryoptions (e.g., try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor. Consider megesterol acetate 80-400 mg daily. Consider anabolic steroids such as oxandrolone, or dronabinol (Marinol®) or other cannabinoid, mainlyfor patients who cannot tolerate steroids or are at high risk to progress. For additional supportive care see NCCN guidelines (*see Appendix 8*).	Selinexor may be skipped intermittently while supportive medications are instituted, usuallyfor < 1 week.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3	See guidelines for Grade 2 anorexia above	Interrupt dosing with selinexor. Restart selinexor at 1 dose level reduction *(see Table 1)* once anorexia resolves to Grade ≤ 2 and patient is clinicallystable.
Grade 4 (anorexia only)	See guidelines for Grade 2 anorexia above	Stop dosing of selinexor. Restart selinexor at 1 dose level reduction *(see Table 1)* only if anorexia resolves to Grade ≤ 2, patient is clinicallystable other contributing factors have been addressed.
Nausea, Acute (common)		
Grade 1	Ensure adequate caloric intake and assess volume status. Consider alternate 5-HT3 antagonists and/or D2 antagonists as needed. Consider addition of NK1 antagonists. Consider addition of 4-8 mg dexamethasone or equivalent on the day after selinexor.	Maintain dose.
Grade 2	See guidelines for Grade 1 nausea above. For additional options see NCCN guidelines for antiemesis (*see Appendix 7*).	Selinexor may be skipped intermittently while supportive medications are instituted, usuallyfor <1 week.
Grade 3	See guidelines for Grade 1 nausea. For additional options see NCCN guidelines for antiemesis (*see Appendix 7*).	Interrupt selinexor dosing until resolved to Grade ≤ 2. For first occurrence of Grade 3, if adequate supportive care resulted in nausea improve to Grade ≤ 1 within 3 days, restart selinexor at current dose. Otherwise, restart selinexor one dose level lower (*see Table 1*). If nausea stabilizes for at least 4 weeks at Grade ≤ 1, original dose of selinexor may be resumed.
Hyponatremia (common)		
Grade 1 (sodium levels < Normal to 130 nM)	Ensure that 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 1-2 times per day.	Maintain dose.
Grade 3 (sodium levels 126-129 nM) without Symptoms	Ensure that 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 2-3 times per day.	Hold selinexor until Grade ≤ 1 (≥ 130 nM), restart on the same dose level.
Grade 3 (120-125 nM) or Grade 4 or Grade 3 with Symptoms	Correct sodium as per institutional guideline Initiate salt supplementation 2-3 times per day.	Hold selinexor until resolved to Grade ≤ 1 (≥ 130nM) then reduce selinexor dose by1 level (See Table 1). For Grade 3 hyponatremia, if serum sodium stabilizes to grade ≤ 1 for at least 4 weeks, original dose of selinexor may be resumed.
Diarrhea (common)		
Grade 1+2	Diet recommendation as per guidelines (Benson, 2004)[b]. Institute standard anti-diarrheal therapy. After the first occurrence of diarrhea, loperamide 2 mg should be considered prophylacticallyapproximately1-2 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 (See Table 1) until resolved to ≤ Grade 1, then re-start at the current dose level.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 3	Institute IV fluids. Diet recommendation as per guidelines (Benson 2004)[b]. Institute standard anti-diarrheal therapy. Once the symptoms resolve to ≤ Grade 1, loperamide 2 mg should be considered prophylacticallyapproximately1-2 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 (See Table 1). If diarrhea stabilizes for at least 4 weeks at Grade ≤ 1, then original dose of selinexor maybe resumed.
Grade 4	Rule out other causes of diarrhea, including infectious agents. In case of opportunistic infection, withdraw all steroids (with tapering if medicallyappropriate) 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 (See Table 1)
Thrombocytopenia[c]		
Grade 1	None	Maintain dose.
Grade 2	Consider implementing platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]) and platelet transfusions, per institutional guidelines. Monitor platelet counts weekly.	
Grade 3 Thrombocytopenia Without bleeding	Initiate platelet growth factors (eltrombopag or romiplostim +/- oprelvekin [IL-11]) and platelet transfusions per institutional guidelines. Monitor platelet counts at least weekly.	In general selinexor dose should be reduced one dose level (see See Table 1*).* In certain cases when there is significant disease involvement in the bone marrow (e.g., in heavily pretreated multiple myeloma) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Sponsor maydecide to continue Selinexor dosing, provided that platelet counts and bleeding symptoms/signs are closelymonitored.
Grade 4 Thrombocytopenia Without bleeding	Follow guidelines (above) for Grade 3 thrombocytopenia without bleeding. Transfuse as per institutional guidelines.	In general, hold selinexor dos until platelet counts >50,000/mm^3 or baseline, then resume selinexor dosing at one dose level lower (See Table 1). In certain cases when there is significant disease involvement in the bone marrow (e.g., in heavily pretreated multiple myeloma) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the Investigator in consultation with the Sponsor may decide to continue Selinexor dosing, provided that platelet counts and bleeding symptoms/signs are closelymonitored.
≥ Grade 3 Thrombocytopenia with bleeding	Transfuse as per institutional guidelines. Follow guidelines for Grade 3 thrombocytopenia without bleeding.	Hold selinexor dosing until platelet counts >50,000/ mm^3 or baseline, then resume selinexor dosing at one dose level below (See Table 1)
Neutropenia		
Grade 3 Neutropenia without fever	Implement growth factors per institutional guidelines until neutrophils are consistently > 1,500/mm^3.	Maintain dose.

Toxicity and Intensity	Supportive treatment	Selinexor Dose Modification
Grade 4 Neutropenia without fever	Implement growth factors per institutional guidelines.	Reduce selinexor dose byone level (See Table 1). After implementation of growth factors, for patients who achieve neutrophil levels > 1,500/mm^3 for > 4 weeks (in the presence or absence of growth factors), selinexor dose maybe re-escalated, with frequent monitoring implemented.
Grade 3 or 4 Neutropenia with fever (febrile neutropenia)	Implement growth factors per institutional guidelines. Implement broad anti-microbial coverage per institutional guidelines. Please note that selinexor has not been associated to date with any opportunistic infections	Hold selinexor until fever resolves and patient is clinicallystable. When patient is clinically stable, restart dosing one dose level lower (See Table 1) After implementation of growth factors, for patients who achieve neutrophil levels >1,500/mm^3 for >4 weeks, selinexor dose may be re-escalated, provided frequent monitoring is implemented.
Other Selinexor-related Adverse Events[d]		
Grade 1 or 2	Initiate standard supportive care per institutional guidelines.	Maintain dose.
Grade 3	Initiate standard supportive care and follow institutional guidelines.	Delay dose until resolved to Grade ≤ 1 or baseline, then reduce by one dose level (See Table 1)
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 (See Table 1)

All dose modifications should be based on the worst preceding toxicity.

[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] Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Onc 2004; 22:2918.

[c] 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.

9.2.3. Dose Reductions for Renal Impairment

Because the impact of renal dysfunction on Selinexor is not known, patients with GFR <30mL/min are not eligible to enter the study. Refer to dose adjustment guidelines below for renal dysfunction that develops while on study and unrelated to Selinexor.

Dose Adjustment Guideline for renal dysfunction while on study

Renal Dysfunction	Recommended Action
Normal to Moderate (GFR ≥ 30 mL/min)	• Full dose
Severe (GFR < 30 mL/min)	• Reduce Selinexor by 30% for at least two weeks • If reduced dose is well tolerated, or GFR increases to >30mL/min, then Selinexor may be increased to starting dose after consultation with the Principal Investigator.

9.2.4. Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled infections should have selinexor treatment withheld until the infection has clinically resolved or is controlled. After the infection is controlled, treatment 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 but the infection must be *clinically* stabilized prior to restarting selinexor.

For patients with recurrent episodes of complicated febrile neutropenia, follow the guidelines outlined in the table above: "**Dose adjustment guidelines for hematologic selinexor-related toxicities".**

9.2.5. Conditions Not Requiring Selinexor Dose Reduction

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

- Grade 3 nausea, vomiting or diarrhea (unless persisting > 3 days with adequate treatment of anti-emetics or anti-diarrheals
- Alopecia of any grade
- Weight loss of less than 20%
- Electrolytes abnormalities that are reversible with oral supplements or brief intravenous infusions.

9.2.6. Missed or Vomited Doses

Missed doses during the week may be replaced within 24 hours. If the dose was missed for more than 24 hours, the dose will be skipped and the next dose will be taken as per schedule. Doses

should not be administered less than 36 hrs apart and all missed doses should be documented in the patient diary.

If a dose is vomited within one hour of ingestion, it will be considered a missed dose and recorded as such on the patient diary. The dose will not be repeated that same day but the patient will follow regular schedule starting the next study dosing day. If vomiting occurs more than 1 hour after dosing, it will still be considered a complete dose.

9.2.7. Delays, Modifications and Reintroduction

All delays, modifications, and reintroductions of Selinexor dosing will be made in consultation with the Principal Investigator.

9.3. Concommitant Medications

9.3.1. Medications for the Prevention of Pregnancy

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.

9.3.2. Use of Blood Products

During the administration of Selinexor, patients may receive red blood cell (RBC) or platelet transfusions for disease or selinexor-related anemia or thrombocytopenia, if clinically indicated, and as per institutional guidelines. Also see guidelines for managing grade 3/4 thrombocytopenia and bleeding complications in the table above ("Dose adjustment guidelines for hematologic selinexor-related toxicities").

9.3.3. Glucocorticoid Therapy

Glucocorticoids ≤ 10 mg oral prednisone (or equivalent) per day are permitted for non-malignant conditions (i.e., asthma, IBD, etc.) as needed.

9.3.4 Required 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 2-3 times daily thereafter, as needed.

9.3.5 Supportive Care for Anorexia, Nausea/Vomiting, and Fatigue

Supportive measures for optimal medical care should be provided to patients during participation in this study. Based on clinical observations in over 550 adult patients treated with selinexor as of 1 December 2014, the main side effects have been primarily related to anorexia with poor caloric

and fluid intake, fatigue, and nausea. .In addition to required 5-HT3 prophylaxis (see Section 9.3.4), anti-nausea/anti-emetic therapy, acid suppression (proton-pump inhibitors [PPI] and/or H2-blockers) and other treatments may be administered as follows:

- Appetite stimulants: megesterol acetate at a dose of 400-800 mg daily.
- Nausea/vomiting and anorexia: Management as per the National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines. See Apendix 7 (NCCN Guidelines for use of anti-emetics) and Appendix 8 NCCN Guidelines for management of anorexia/cachexia).
- 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.

Supportive care guidelines for managing AEs are provided in Section 9.2.2, Table .

9.3.6 Dietary and Concomitant Medication Restrictions

Medications: 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.

Diet: There are no dietary restrictions on this study.

9.4. Prohibited Concomitant medications

Concurrent therapies: Concurrent therapy with glucocorticoids is allowed, as specified in Section 9.3.3.

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

Medications: 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 Section 20.5 (Appendix 5) for a list of representative products. Patients must report all prescription and non-prescription medicines to their physicians during this study.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Evaluation during treatment: Screening and Cycle #1					
	D-21 to -1	D1	D7 (+/-3 Days)	D14(+/- 3 Days)	D21 (+/- 1 D)
Written Informed Consent	X				
Medical History & Prior Cancer Treatments (1)	X				
Complete Physical Examination, Oxygen saturation	X	X		X	
Weight, Blood Pressure, Pulse, Temperature	X	X	X	X	X
12-lead Electrocardiogram (ECG) (2)	X			X	
Serum Pregnancy Test (within 7 days of dosing)	X				
Urinalysis (& microscopy if indicated) (3)	X				
Complete Serum Chemistry (4)	X	X	X	X	X
Thyroid Stimulating Hormone (TSH)	X				
Coagulation tests (PT, INR, aPTT) (5)	X		X	X	X
CBC with Differential & Reticulocyte Count (6)	X	X	X	X	X
Chest Radiograph (7)	X				
Ophthalmology exam(12)	X				
Bone marrow samples for routine disease assessments (11)	X				X
Blood samples for pharmacodynamic assays (10)	X	X	X	X	X
Bone marrow samples for pharmacodynamic assays (10)	X			X	X

Selinexor dosing [8]		2 doses per week for two weeks, followed by one week of no therapy			
Adverse Events		X	X	X	X
Concomitant Medications	X	X	X	X	X

Evaluation during treatment: Cycle 2, 3, 4, etc., and at End of Study				
	D 1	D 14 (+/- 3 days)	D 21 (+/-1 day)	End of Study Visit Within 30 (±7) days post last dose
Complete Physical Examination	X			X
Weight	X	X		X
12-lead Electrocardiogram (ECG)[2]	X			
Pregnancy Test (within 7 days of dosing)	X			X
Serum Chemistry	X	X		X
Coagulation tests (PT, INR, aPTT)	X			X
CBC with Differential, reticulocyte count	X	X	X	X
Blood and bone marrow tests for pharmacodynamic assays (blood and BM pre-dose and blood 4 hours post-dose)			X (cycles 2 & 4)	X
Bone marrow tests for response assessment			X (cycles 2, 4 then every other cycle until CR or max response, and when clinically indicated)	X
Selinexor dosing [8]	2 doses per week for two weeks, followed by one week of no therapy			

Adverse Events	X	X		X
Ophthalmology exam[12]	-[12]	-[12]	-[12]	-[12]
Concomitant Medications	X	X		X

Treatment calendar notes and event windows

Cycle 1 day 1 must begin within 5 working days of registration.

All screening evaluations are to be performed within 21 days (Day -21 to -1) prior to cycle 1 day 1.

All serum chemistry and CBC with differentials results must be reviewed and assessed by the investigator prior to all Selinexor administration for cycle 1. Chemistry labs do not have to be repeated if they have been performed within 1 week prior Selinexor administration (except for screening labs).

For cycles 2 and beyond, day 1- a CBC must be completed and results must be reviewed by study investigator before patients take first dose for that cycle.

End of Study visit is to be performed within 30 ± 7 days following patient's last drug administration. If, in the judgment of the investigator, the patient requires immediate anti-cancer therapy, the final visit may be conducted earlier than 30 days and should preferably be completed prior to patient receiving any additional therapy.

Patients will receive selinexor twice weekly, dosed at least 36 hours apart orally at a starting dose of 60mg per dose. Selinexor will be given for 2 weeks, followed by 1 week of no therapy.

Patients will undergo a baseline ophthalmologic exam by either their personal Ophthalmologist or by an MSKCC Ophthalmologist to document any pre-existing conditions. If vision changes occur on study, the baseline exam will be used to detect any new pathology, but serial exams are not mandated

All physical examinations must be performed by an MD or Nurse Practitioner listed on the face sheet for this study.

Study Assessments Footnotes

1. **Medical History & Prior Cancer Treatments:** includes detailed history of prior cancer therapies including start and stop dates, and disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

2. **ECGs:** to be performed in a supine position at screening, then bi-weekly during cycle 1 (pre-dose). For cycles 2 and beyond, EKG will be done pre-dose on day 1 of each cycle. ECGs do not have be repeated if one was performed within 1 calendar day prior to visit.

3. **Urinalysis (& microscopic exam if clinically indicated):** include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, urobilinogen, and microscopic examinations if any of the preceding urinalysis tests are abnormal. Urine samples will be obtained at screening and during the study only if clinically indicated. Urine microscopy will be done only if urinalysis results are considered clinically significant by investigator.

4. **Complete Serum Chemistry**: include Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, and Glucose, Calcium, Phosphate, Magnesium, ALT, AST, Alkaline Phosphatase, Total Bilirubin, LDH, Total Protein, Albumin, and Uric acid. Chemistry tests are to be performed at screening, weekly during cycle 1, and every 2 weeks during cycle 2 and beyond, and at the off-study visit. May be performed at MSKCC or local laboratory.

5. **Coagulation:** include Prothrombin Time (PT), international normalization ratio (INR), and activated Partial Thromboplastin Time (aPTT) which will be performed at screening, during cycle 1 on days 7 (+/- 3 day), and 21 (+/- 3 day). For cycles 2 and beyond, coagulation studies are to be performed on day 1 (+/- 3 days) and at the final visit. For patients being treated with warfarin (Coumadin), these coagulation tests are to be performed and monitored twice a week during the first two cycles and anytime the dose of Selinexor is adjusted. If the INR is stable after the first two cycles, then monitoring may revert to once per cycle on day 1**.** May be performed at MSKCC or local laboratory.

6. **CBC with differential and reticulocyte count**: include hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, reticulocytes, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual. May be performed at MSKCC or local laboratory.

   CBC with differentials to be performed at screening, cycle 1 day 1, and on days 7, 14, 21 (+/- 1 day), cycles 2 and beyond on days 1, 14 (+/- 3 days), or more often as clinically indicated, and at the End of Study visit.

7. **Chest Radiograph:** both posteroanterior and lateral films should be obtained at baseline. Note: this test does not need to be repeated if results are available from a CT of chest or chest X-ray (PA and laeteral views) performed 30 days prior to C1D1. This test is done to ensure the absence of active pulmonary disease prior to therapy and as a baseline for comparison in the event that patients develop pulmonary adverse effects during the study.

8. Selinexor Drug Administration: patients will receive selinexor twice weekly

orally at a starting dose of 60mg per dose. Selinexor will be given for 2 weeks, followed by 1 week of no therapy. The scheduled dosing days should be the same days in each week. One cycle is 21 days or 4 doses (with the following week off).

9. Blood and bone marrow tests for pharmacodynamics: blood samples (7ml EDTA, 2ml EDTA, and/or PAXgene)
and bone marrow samples will be obtained for research assessments at baseline, cycle 1 day 7 (PB only; +/- 2 days, and after 2 doses of Selinexor), cycle 1 day 14 (PB and BM; +/- 3 days), cycle 1 day 21 (PB and BM; +/- 3 days and before dosing starts for cycle #2), and PB and BM day 21of cycle 2 and 4, and at the time of the End of Study bone marrow.
The day 14 bone marrow specimens will be obtained on the first 10 patients. For details regarding the samples and assays at these time points, see the Karyopharm Laboratory manual (for analyses done at Karyopharm), and see Section 10.4 for a description of the PD analyses to be done in the MSKCC Pathology Core Laboratory, and the laboratory of Dr. Andreef and Dr. Schwartz. In the event a patient is not dosed during a protocol visit, the visit will be rescheduled to reassess the patinet's condition, and in order to obtain all required research samples. The patient will continue their subsequent visits as planned. Additionally, if a patient's dose is held to reassess their disease status, research pharmacodynamic samples will be held until disease status is confirmed, or at the discretion of the treating investigator.

10. Bone marrow tests for disease assessments: Bone marrow aspirate and biopsy will be performed at baseline, on day 1 of cycle 2 (same as cycle #1, day 21), and on day 21 of cycles 2, and every other cycle therafter until CR or maximal response is achieved, at the time of disease progression, and at the End of Study visit (for patients coming off study for reasons other than disease progression).

11. **Ophthalmology exam:** A full ophthalmological exam, by an ophthalmologist, is required of all patients at screening, and if clinically indicated during study. The following criteria will be followed:
    1. Prior to dilation:
        - Best corrected visual acuity
        - Slit lamp examination including tonometry
    2. Dilated:
        - Fundoscopy
        - Slit lamp examination to document lens clarity

If a cataract is seen during the exam, it will be graded according to the Lens Opacities Classification System (LOCS III; (See Section 20.6, Appendix 6).

10.2 Efficacy assessments

Efficacy will be assessed by evaluation of bone marrow aspirates and biopsies, complete blood counts, and transfusion records. Hematologic Improvement will be assessed continuously, with the use of CBC values and transfusion records. At the time of bone marrow aspirates and biopsies, full efficacy evaluations will be performed, taking into account blood and bone marrow parameters, and responses will be assessed using the 2006 Modified MDS International Working Group Response Criteria. All efforts should be made to obtain bone marrow studies at the End of Study visit.

10.3 Safety assessments

Safety will be assessed continuously by monitoring for new or worsening subjective symptoms, physical exam findings, and laboratory values. For details on Adverse Event collection and reporting, please see Section 17.2.

10.4 Pharmacodynamic (PD) Studies

PD schedule:

Blood samples and bone marrow samples will be obtained for research assessments at the following timepoints:

Baseline, day -21 to -1: Blood and bone marrow samples for PD studies at time of routine disease assessment (for Karyopharm, Dr. Schwartz, Dr. Andreef, MSKCC Pathology Laboratory).

Cycle 1 day 1: PD samples at pre-treatment, 4 hours, and 8 hours post dose (Karyopharm)

Cycle 1 day 7 (+/-1 day): Pre-dose blood samples (7ml EDTA x2) for PD studies at time of routine bloodwork (Dr. Schwartz)

Cycle 1 day 14 (+/- 3 days): Blood samples at time of routine bloodwork for PD studies. BM aspirate and biopsy (for first 10 patients only) for PD research studies (for Karyopharm, Dr. Schwartz, Dr. Andreef, MSKCC Pathology Laboratory)..

Cycle 1 day 21 (+/- 1 day): Before dosing starts for cycle #2 and at time of routine disease assessment.PB and BM aspirate and biopsy for PD studies (Karyopharm, Dr. Schwartz, Dr. Andreef, MSKCC Pathology Laboratory)

Cycle 2 and 4, day 21 (+/-1 day): At time of routine disease assessment; PB and BM aspirate for PD studies (Karyopharm, Dr. Schwartz, Dr. Andreef, MSKCC Pathology Laboratory)

At the time of the End of Study bone marrow (At time of routine disease assessment): PB and BM aspirate for PD studies (Karyopharm, Dr. Schwartz, Dr. Andreef, MSKCC Pathology Laboratory)

<u>Pharmacodynamic Studies:</u>

Dr. Gary Schwartz: blood and bone marrow aspirates will be shipped to Dr. Schwartz's laboratory at Columbia University for studies to assess the mechanism of selinexor. His laboratory will perform the following analyses: Western blots for XPO1, p53, p21, PARP, and caspase. Specimens will be processed using ficoll-hypaque separation at the HOTB. Bone marrow and blood mononuclear cells will be viably cryopreserved (in DMSO) and stored until they are batch-shipped approxiamately once

each month on dry ice to the laboratory of Dr. Schwatrz at Columbia University c/o Shyamprasad Deraje Vasudeva via FedEx (account number 2346-5338-5).at the following address:

Columbia University
1130 Saint Nicholas Ave
ICRC Room 207, Schwartz Lab
New York, NY 10032

MSKCC Surgical Pathology:
Dr. Sen will direct the processing of bone marrow immunohistochemical (IHC) stains, which will be performed by the Pathology Core Laboratory at MSKCC to assess nuclear localization of beta catenin and p65, thereby assessing for evidence of WNT and NF-kB pathway signaling activation, respectively. Bone marrow specimens will be processed routinely for response assessment at the designated time points as per the protocol. Specimens will be directed to Dr. Filiz Sen. Extra sections will be obtained under the direction of Dr. Filiz Sen, and the Core Laboratory will perform.IHC for nuclear beta catenin and p65 using standard IHC techniques. .

Dr. Michael Andreef (MD Anderson Cancer Center):

Dr. Andreef will assess nuclear and cytoplasmic p53 localization on unstained bone marrow aspirate smears. Bone marrow aspirate slides are prepared at the time of the bone marrow procedure as per standard routine. No processing is required. These slides will be delivered to Dr. Klimek and will be stored at room temperature until they are batch-shipped by UPS approxiamately every three months at ambient temperature in plastic slide carriers to Dr. Andreef. Specimens will be sent to the attention of Teresa Mcqueen (using Fedex accout # 136495291) at the following address:

Name: Teresa Mcqueen
Company: MD Anderson Cancer Center
Address: 6767 Bertner Ave.
T6.3948
Houston Tx 77030

Karyopharm:
Karyopharm will perform functional assays to assess NFkB and WNT pathway signaling and cytokine levels. Blood and bone marrow samples will be delivered to the MSKCC HOTB for centrifugation, aliquotting and storage to be batched-shipped to Karyopharm. Details are provided in the Karyopharm laboratory manual.

11.1 TOXICITIES/SIDE EFFECTS

Side effects observed in patients include:

COMMON, SOME MAY BE SERIOUS
In 100 people receiving selinexor, more than 20 and up to 100 may have:

- Nausea and/or vomiting
- Fatigue or loss of energy
- Loss of appetite
- Diarrhea

- Weight loss
- Low platelets
- Decrease in red blood cells
- Low sodium

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving selinexor, from 4 to 20 may have:

- Change in taste
- Dehydration
- Dizziness
- Constipation
- Confusion
- Shortness of breath
- Visual changes including blurred vision
- Low neutrophil count
- Low white blood cell count
- Increased creatinine
- Dry mouth
- Sepsis

RARE, AND SERIOUS

In 100 people receiving selinexor, 3 or fewer may have:

- worsening cataract
- Febrile neutropenia
- Fainting
- Cognitive disturbance
- Altered balance
- Acute cerebellar syndrome – symptoms can include a sudden loss of coordination
- Pneumonia

Reproductive risks

Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important patients understand the need to use birth control while on this study.

Adverse Events Reporting

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. An abnormal laboratory value will not be assessed

as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary and secondary efficacy endpoints of this study will be assessed using the 2006 Modified MDS International Working Group response criteria (Cheson et al., 2006).

Patients will be eligible for the primary efficacy endpoint if they have undergone at least one cycle of therapy, and are evaluable for response. Patients will be evaluable for Hematologic Improvement with the availability of CBC parameters and transfusion records, and will be evaluable for all response categories if they undergo at least one bone marrow procedure (first planned marrow for response assessments is after dosing is completed for the first 21-day cycle).

For the primary endpoint, overall CR, marrow CR, and PR, and HI responses will be tabulated.

According to the 2006 Modified MDS International Working Group response criteria, response categories include the following:

Complete Remission (CR)
Bone marrow evaluation: Repeat bone marrow showing 5% or less myeloblasts with normal maturation of all cell lines. Persistent dysplasia will be allowed but noted.

Blood:

Hgb $\geq$ 11 g/dL (untransfused, patient not on erythropoietin)
Neutrophils $\geq$ 1.0 x 10^9/L or more (not on myeloid growth factor)
Platelets $\geq$ 100 x 10^9/L or more (not on thrombopoietic factor)
Blasts 0%

CBC values must last at least 1 month. In some circumstances, protocol therapy may require the initiation of further treatment before the 1 month period. Such patients can be included in the response criteria into which they fit at the time therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the pervious course.

Partial Remission (PR)
All the CR criteria except:
Bone marrow evaluation: Blasts decreased by 50% or more over pretreatment, but still more than 5%.
CBC values must last at least 1 month unless interrupted by therapy as described above.

Marrow CR
Bone Marrow: 5% myeloblasts or less and decreased by 50% or greater over pretreatment.
Blood: if criteria for HI responses are met (see criteria below), they will be noted in addition to marrow CR

Stable Disease

Failure to achieve at least a PR, but with no evidence of progression for at least 2 months

Failure
Death during treatment or disease progression characterized by worsening of cytopenias, or progression to AML.

Relapse after CR or PR

One or more of the following:
- Return to pretreatment bone marrow blast percentage
- Decrement of 50% or greater from maximum remission / response levels in granulocytes or platelets
- Reduction in hemoglobin concentration by at least 1.5 g/dL or new/recurrent transfusion dependence (in the absence of another explanation such as treatment effect, acute infection, gastrointestinal bleeding, hemolysis, etc.)

Disease Progression
- For patient with less than 5% blasts: a 50% or more increase in blasts to more than 5% blasts
- For patients with 5% to 10% blasts: a 50% or more increase to more than 10% blasts.
- For patients with 10% to 20% blasts: a 50% or more increase to more than 20% blasts
- For patients with 20% to 30% blasts: a 50% or more increase to more than 30% blasts.
- One or more of the following: 50% or greater decrement from maximum remission/response levels in granulocytes or platelets, reduction in hemoglobin concentration by at least 2 g/dL, or transfusion dependence (in absence of another explanation such as acute infection, G.I. bleeding, hemolysis etc.)

Hematologic Improvement (HI)

Improvements must last at least 2 months in the absence of ongoing cytotoxic therapy. When protocol therapy requires the initiation of further treatment before the 2 month period, patients can be included in the response criteria into which they fit at the time therapy is re-started.

Hematologic improvement should be described by the number of individual, positively affected cell lines (eg, HI-E; HI-E + HI-N; HI-E + HI-P + HI-N)

Hematologic Improvement response categories include the following:

- Erythroid response (HI-E)
  For patients with pretreatment hemoglobin less than 11g/dL:
  - Hemoglobin increase by $\geq$ 1.5 g/dL
  - Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC/8wk compared with the pretreatment transfusion number in the pervious 8 wk. (*)

  (*) Only RBC transfusions given for Hgb < 9.0 g/dL will count in the RBC transfusion response evaluation.

- Platelet response (HI-P)

  For patients with a pretreatment platelet count < 100 x 10^9/L:

An absolute increase of $\geq$ 30 x 10^9/L or more for patients starting with > 20 x 10^9/L platelets

An increase from < 20 x 10^9/L to > 20 x 10^9/L, and by at least 100%.

- Neutrophil response (HI-N)

  For patients with pretreatment neutrophil count < 1.0 x 10^9/L: At least a 100% increase and an absolute increase > 0.5 x 10^9/L.

Progression/relapse after HI

One or more of the following:

- A 50% or greater decrement from maximum response levels in granulocytes or platelets
- A reduction in hemoglobin concentration by at least 1.5 g/dL
- Transfusion dependence (in the absence of other explanation, such as hemolysis, hemorrhage, etc).

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. Patients who discontinue from the study will be encouraged to return to the study site to undergo the evaluations listed for the End of Treatment Visit.

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

- Due to disease progression
- Noncompliance with study procedures
- Need of treatment with medications not allowed by the study protocol
- Patient no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- For the third occurrence of the same Grade ≥3 non-hematological toxicity
- For the third episode of clinically significant bleeding or fourth episode of complicated febrile neutropenia
- Investigator discretion
- Other treatments become available which are more appropriate for the individual patient

To the extent possible, patients must strictly follow the standard dosing schedule. Patients who miss 3 doses or more (out of 4 doses) in a cycle in the absence of study drug related toxicity will be discontinued.

If the reason for withdrawal is the occurrence of an AE, the patient will be followed by the Investigator until such events resolve, stabilize, and according to the Investigator's judgment there is no need of further follow-up. The reason for withdrawal from the study will be documented in the case report form.

14.1 BIOSTATISTICS

Primary endpoint evaluation

The primary endpoint of this study is to investigate the efficacy of Selinexor in patients with MDS refractory to hypomethylating agents (decitabine and/or 5-azacytidine). The standard treatment in this setting is supportive care, where the response rate is assumed to be zero. Therefore, in this population, a response rate of 25% would be considered promising, whereas a 5% response rate would not be considered promising. For purposes of assessing the primary endpoint, response categories will include CR, PR, marrow CR (mCR), or Hematologic Improvement. Using a Simon's two-stage minimax design, this trial will accrue a maximum of 20 patients. Early termination may occur if no responses are observed in the first 13 patients. If at least one response is observed, the trial will continue to the maximum sample size. At the end of the trial, the treatment strategy will be considered promising in this patient population if at least 3 patients achieve a response. The type I and type II errors are set at 0.10.

The response evaluation cohort will include those patients who have completed at least 3 of 4 planned doses of their first cycle of therapy and have undergone at least one full scheduled post-treatment disease assessment (informative bone marrow aspirate or biopsy, cytogenetics, and CBC with differential). For patients who come off study after completing at least 3 of 4 planned doses of their first cycle of therapy and are unable to undergo (or refuse) a bone marrow procedure, an assessment for Hematologic Improvement (based on CBC data) will be performed and described and an attempt will be made to obtain follow-up CBC data for the 8 weeks mandated to confirm Hematologic Improvement according to the MDS International Working Group response criteria. Patients who come off study after starting study drug because of toxicity, death, or withdrawal of consent prior to undergoing a response assessment will not be replaced and will be considered a treatment failure. Patients who enroll on study but do not receive study therapy will be replaced.

Analysis of secondary endpoints

1. Response duration will be caluated among patients who achieve a response of HI, mCR, PR or CR using Kaplan-Meier methodology. Median duration of response and the corresponding 95% confidence interval will be estimated.
2. The frequency of stable disease will be tabulated and exact 95% confidence intervals will be estimated.
3. The response rate and response duration will also be described for the generally poor-risk therapy-related MDS patients enrolled on this study (therapy-related MDS accruals may approach ~ 50%, as seen in MSKCC protocol 06-054). The response rate will be estimated along with an exact 95% confidence interval to evaluate the proportion of patients who have

CR, PR, mCR or HI. Median response duration and corresponding 95% confidence intervals will be estimated.

4. Overall survival from the time of study enrollment will be caluated using Kaplan-Meier methodology. Overall survival curves will be displayed for the study population along with selected quantiles and corresponding 95% confidence intervals of survival.
5. Since Selinexor may require chronic dosing to maintain its effect, the overall tolerability and safety of chronic Selinexor dosing will be described on patients throughout all cycles of treatment who have received at least 1 dose of selinexor. Tolerability will be assessed by calculating the proportion of patients who withdraw consent due to chronic low-grade (1/2) toxicity. Safety will be calculated by determining the proportion of patients who have any toxicity listed in section 11.0. This will be calculated overall at each treatment cycle and separately by the Selinexor dose received at the time of the selected toxicity. Proportions and exact 95% confidence intervals will be calculated.
6. Descriptive statistics will be used to explore the relationship between the results of the pharmacodynamics studies and therapeutic response or study entry disease parameters. The Wilcoxon rank-sum statistic or Fisher's exact test may be used to assess these associations.

Accrual rates and study duration

It is expected that the study will accrue 1-2 patients per month, resulting in completion of accrual in 10-20 months.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

This is an open-label phase 2 study.No randomization will be performed.

16.1 DATA MANAGEMENT ISSUES

A research study assistant (RSA) will be assigned to study. The responsibilities of the RSA include project compliance, data collection, extraction and data entry, data reporting, coordination of the activities of the protocol study team and, and of the flow of regulatory paperwork. Study accrual is estimated to to take 1.5 years, and it is estimated that the study will be complete approximately 9 months from the date of the last registration.

The data collected for the study will be entered into a secure database (CRDB). All routine blood test results required per the protocol will be captured in CRDB in addition to baseline medical conditions and disease information, response assessments, off-study documentation, and toxicity grade and attribution. Source documentation will be available to support the computerized patient record.

Lab toxicities will be routinely assessed by the PI. The following labs are considered common toxicities for the disease under study and therefore should be considered not clinically relevant for data entry purposes.

- Total WBC Count

The total WBC count is typically decreased due to the disease process. However, further reductions in the WBC count are not clinically relevant. Reductions in other WBC subsets may be clinically meaningful and will continued to be entered per MSK guidelines.

MSKCC will cross-reference Karyopharm's IND and will be responsible for all safety monitoring. All SAEs will be reported to the MSKCC IRB. The safety of the study will be monitored by the MSKCC Data and Safety Monitoring Committee.

16.2 Quality Assurance

Weekly registration reports will be generated by the RSA and reviewed by the PI to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies.

Accrual rates and extent and accuracy of evaluations and follow up will be monitored periodically throughout the study. Recurrent lapses in data collection, deviations or violations will be disussed with the study team and a corrective plan will be generated.
Accrual goals and factors impacting accrual goals will be discussed at the weekly New Patient/Protocol Leukemia meetings.

16.3 Data and Safety Monitoring

The data and safety monitoring plan at Memorial Sloan-Kettering Cancer Center was approved by the National Cancer Institute in September 2001. The plan addressed the new policies set forth by the NCI and the document entitled "Policy of the National Cancer Institute for data and safety monitoring of clinical trials" which can be found at http://grants.nih.gov/grants/guide/notice-files/not98-084.html.

The DSM plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC data and safety monitoring plan can be found on the MSKCC Internet at http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

Memorial Sloan-Kettering Cancer Center has set up three distinct monitoring processes for our clinical trials program. There are two sub-committees of the Center's Institutional Review Board/Privacy Board (IRB/PB) and Research Council (RC) that have the responsibility of data and safety monitoring. These are joint sub-committees with dual-reportin responsibilities. The Data and Safety Monitoring Committee (DSMC) is the sub-committee responsible for monitoring all Phase I, II, I/II, pilot and non-phase clinical trials. The Data and Safety Monitoring Board (DSMB) is the sub-committee responsible for monitoring Phase III randomized clinical trials. The Therapeutic Response Review Committee (TRRC) is the sub-committee of Research Council responsible for the independent therapeutic response review for participants in IRB/PB approved clinical trials where therapeutic efficacy is a stated primary objective, typically phase II and III trials. Formal monitoring of such studies is designed to ensure that the interests of the participants are being scrutinized on a regular basis, and that the trial is progressing in a satisfactory manner.

The Data and Safety Monitoring Committee (DSMC) convenes once per quarter and monitors the risk participants are exposed to, the progress of the study, the adequacy of the data storage and whether sufficient data are being entered into the CRDB. The DSMC monitors phase I, II, I/II, pilot and non-phase trials that are not being monitored by an industrial sponsor, and which meet the NCI definition of a Clinical Trial. This trial will qualify for monitoring by the DSMC.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required, and the monitoring procedures will be established at the time of protocol activation

16.4 Regulatory Documentation

Participating sites that are consulting and/or conducting specimen or data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSKCC.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits and serial safety monitoring. Specific guidelines for symptom management are in place to protect the study participant.

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the all of the inclusion and none of the exclusion criteria will be eligible. Both men and women and members of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study. Also, the majority of children are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Consent process: All patients at MSKCC who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities/Side-Effects: There are risks associated with treatment as described in Section 11.0; however, patients screened for enrollment will be deemed appropriate for treatment independent of this study.

Benefits: It is unknown if selinexor can benefit patients with myelodysplastic syndromes. The goal of this study is to assess if selinexor has the potential to demonstrate objective response in patients with myelodysplastic syndromes.

Costs: Patients will be charged for physician visits, routine laboratory tests, and radiologic studies required for monitoring their condition. The cost of research-only pharmacodynamic studies will be covered by research funds.

Alternatives: For patients considering this trial as second-line therapy, standard second-line treatments would include supportive care or another study drug in an alternate clinical trial, since for patients considering this trial, there are no standard treatment options.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSKCC) and external personnel (Karyopharm, the manufacturer of selinexor), its authorized agents, the FDA, and/or other governmental agencies) may review patient records as required.

Patient safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring board established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1

Reporting to Karyopharm (company holding cross-referenced IND)
In addition to reporting to the FDA, Sponsor-Investigator will forward completed SAE and pregnancy forms to representatives of the Sponsor. Forms will be completed and emailed to pharmacovigilance@karyopharm.com

17.4 Ethics and good clinical practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

17.5 Institutional Review Board

The protocol, Investigator's Brochure, Informed Cconsent Form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, progress reports, and any revisions to these documents will be provided to the MSKCC IRB by the Principal Investigator. Any amendment must be approved after review by the IRB.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

20.1 Appendix 1 : Eastern Cooperative Oncology Group Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	

	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

20.2 Appendix 2: Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0

The CTC version 4.03 is published at the following web address:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

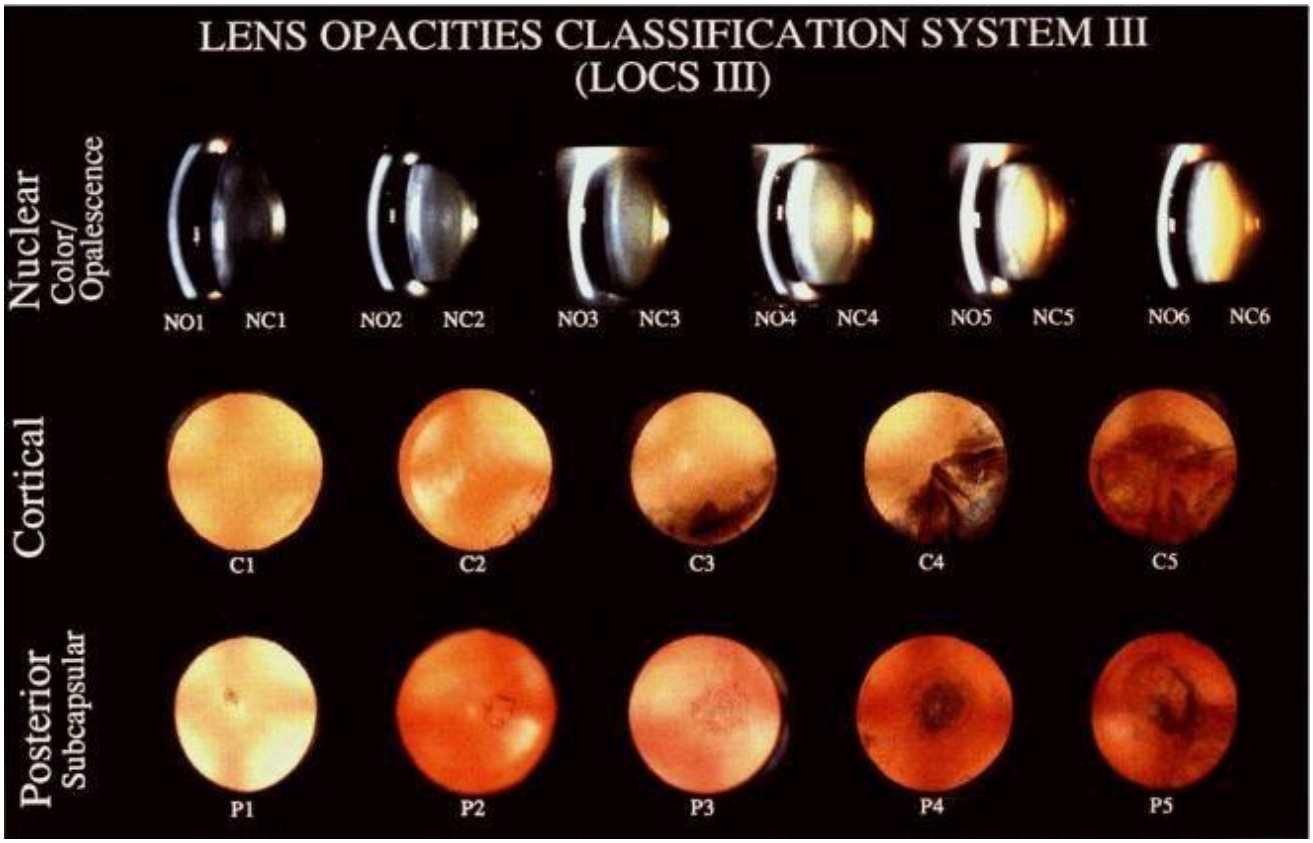
20.3 APPENDIX 3: GLUTATHIONE (GSH)-, S-ADENOSYLMETHIONINE (SAM)-, OR N-ACETYLCYSTEINE (NAC)-CONTAINING PRODUCTS (REPRESENTATIVE LIST)

Product Name	Ingredient	Manufacturer/Brand	Strength	Dose Form	Other key ingredients
Glutathione					
Glutathione	glutathione	NOW Foods	500 mg	Vcaps	milk thistle, alpha lipoic acid
Glutathione	L-glutathione	NOW Foods	250 mg	Vcaps	
Glutathione reduced	glutathione	Jarrow Formulas	500 mg	capsules	
Reduced glutathione sublingual complex	glutathione	Source Naturals	50 mg	sublingual	
Glutathione reduced	glutathione	Bulk Supplements	10, 25, 50, 100, 250, 500, 1000 g	powder	
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	Viva Labs	500 mg	capsules	alpha lipoic acid
Glutathione, Cysteine & C	glutathione, 50 mg L-cysteine, 200 mg vitamin C, 500 mg	Life Extension	750 mg	capsules	L-cysteine, vitamin C
Liposomal Glutathione	glutathione	Empirical Labs	4 mL	liquid	
Lypospheric GSH	glutathione	LivOn Laboratories	450 mg	packet	essential phospholipids from soy lecithin
Ivory Caps Skin Enhancement Formula	glutathione	Princeton Nutritional Systems	1500 mg	capsules	
Glutathione GOLD	S-acetyl glutathione	Health Naturally	200 mg	capsules	
Mega-Liposomal Glutathione	glutathione	Aurora NutraScience	750 mg	liquid	

L-Glutathione 500	L-glutathione	GNC	500 mg	capsules	
N-acetylcysteine (NAC)					
Acetadote for acetaminophen overdose	acetylecysteine	Cumberland Pharmaceutcals	IV	sterile solution, 200 mg/mL	
CerefolinNAC medical food for age-related memoryloss	L-methylfolate vitamin B12 N-acetyl cysteine	PAMLAB, LLC	600 mg NAC	caplets	L-methylfolate vitamin B12
NAC	N-acetyl cysteine	NOW Foods	600 mg	capsules	selenium, molybdenum
N-A-C Sustain	N-acetyl L-cysteine	Jarrow Formulas	600 mg	capsules	
Best NAC Detox Regulators	N-acetyl cysteine	Doctor's Best	600 mg	capsules	selenium, 50 mg molybdenum, 50 mg
S-adenosylmethionine (SAM)					
SAM-e Complete	S-adenosylmethionine	Nature Made	400 mg	tablets	
SAMe	S-adenosyl-L-methionine	NOW Foods	400 mg	tablets	
Double Strength SAMe 400	S-adenosylmethionine	Doctor's Best	400 mg	tablets	
SAM-e 200	S-adenosylmethionine	Jarrow Formulas	200 mg	tablets	
SAMe	S-adenosyl-l-methionine	Source Naturals	400 mg	tablets	
SAMe	S-adenosyl-l-methionine	Source Naturals	200 mg	tablets	
SAMe	S-adenosylmethionine	Natrol	400 mg	enteric coated tablets	
SAMe	S-adenosyl-methionine	NOW Foods	200 mg	tablets	vitamin B-6, folic acid, vitamin B-12

20.4 Appendix 4: Lens Opacities Classification System III (LOCS III)

If a cataract is seen during the slit lamp examination to document lens clarity, the cataract will be graded according to the LOCS III.



Paitent:
MRN:

Ophthamological Exam Assessments

Best Corrected Visual Acuity (BCVA):		
Normal	Abnormal	Description
Adnexa		
Lids		
Lashes		
Conjunctiva		
Cornea		
Ant. Chamber		
Iris		
Lens[1]		
Intraocular pressure		
Fundus		
Vitreous		
Optic Disc[2]		
Macula		
Retina		

[1] Does lens show cataract change? Follow grading system in description

[2] Cup/disc ratio and any abnormalities, if observed

Visit Checklist

Prior to dilation:

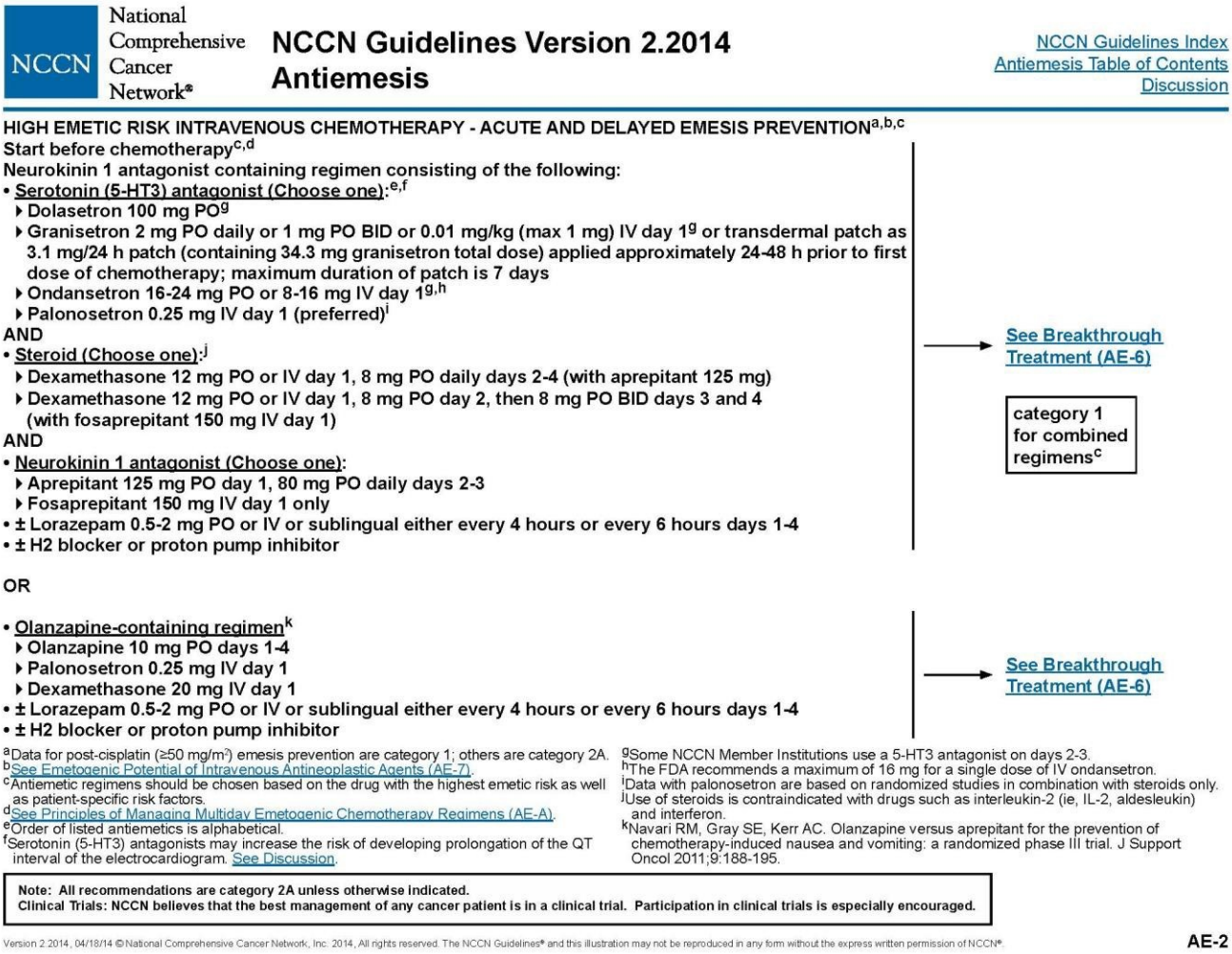
Best corrected visual acuity
Slit lamp examination including tonometry

Dilated:

Fundoscopy
Slit lamp examination to document lens clarity

MD Signature_____ **Date**_____

20.5 Appendix 5: NCCN Clinical Practice Guidelines in Oncology: Antiemesis



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
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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

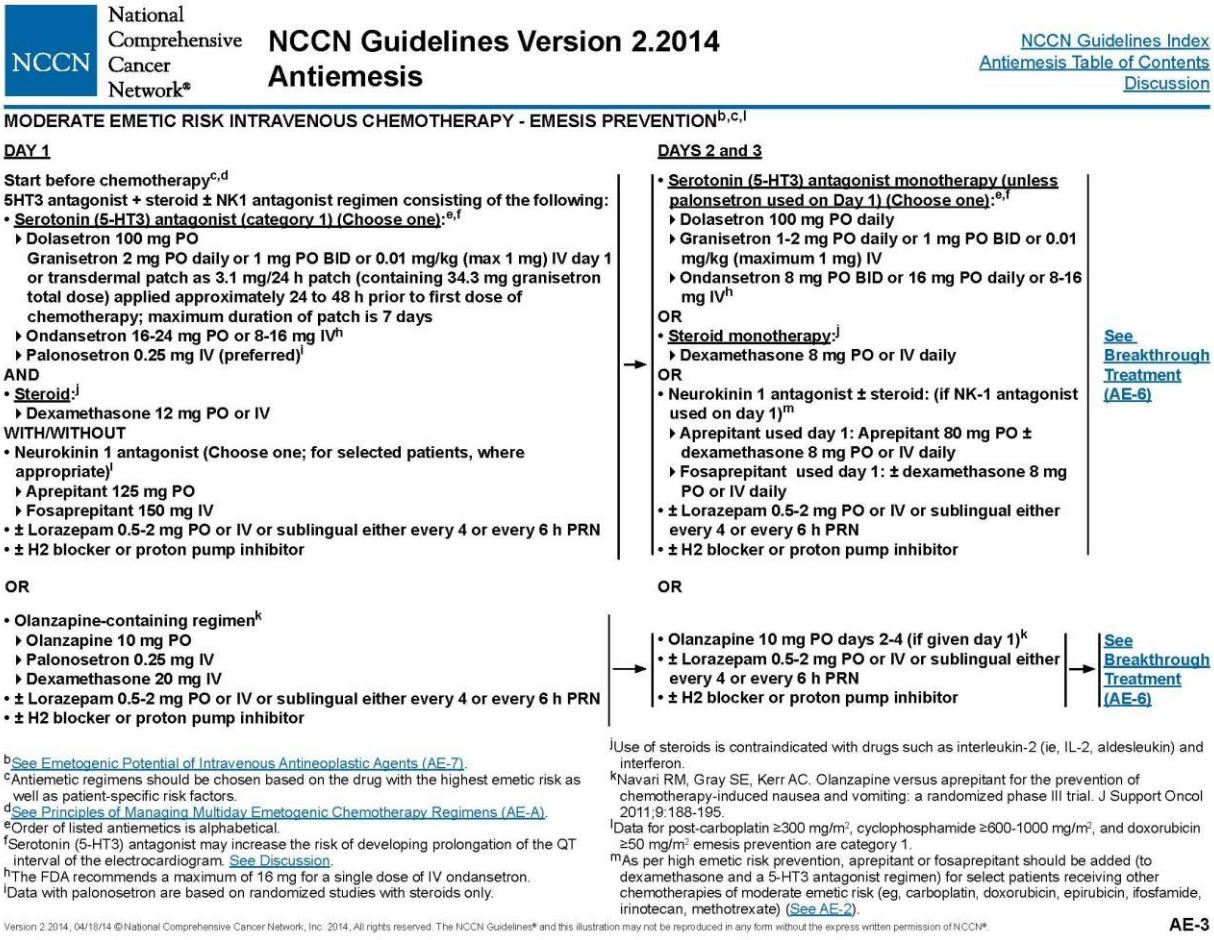
- **Olanzapine-containing regimen[k]**
  - **Olanzapine 10 mg PO days 1-4**
  - **Palonosetron 0.25 mg IV day 1**
  - **Dexamethasone 20 mg IV day 1**
- **± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4**
- **± H2 blocker or proton pump inhibitor**

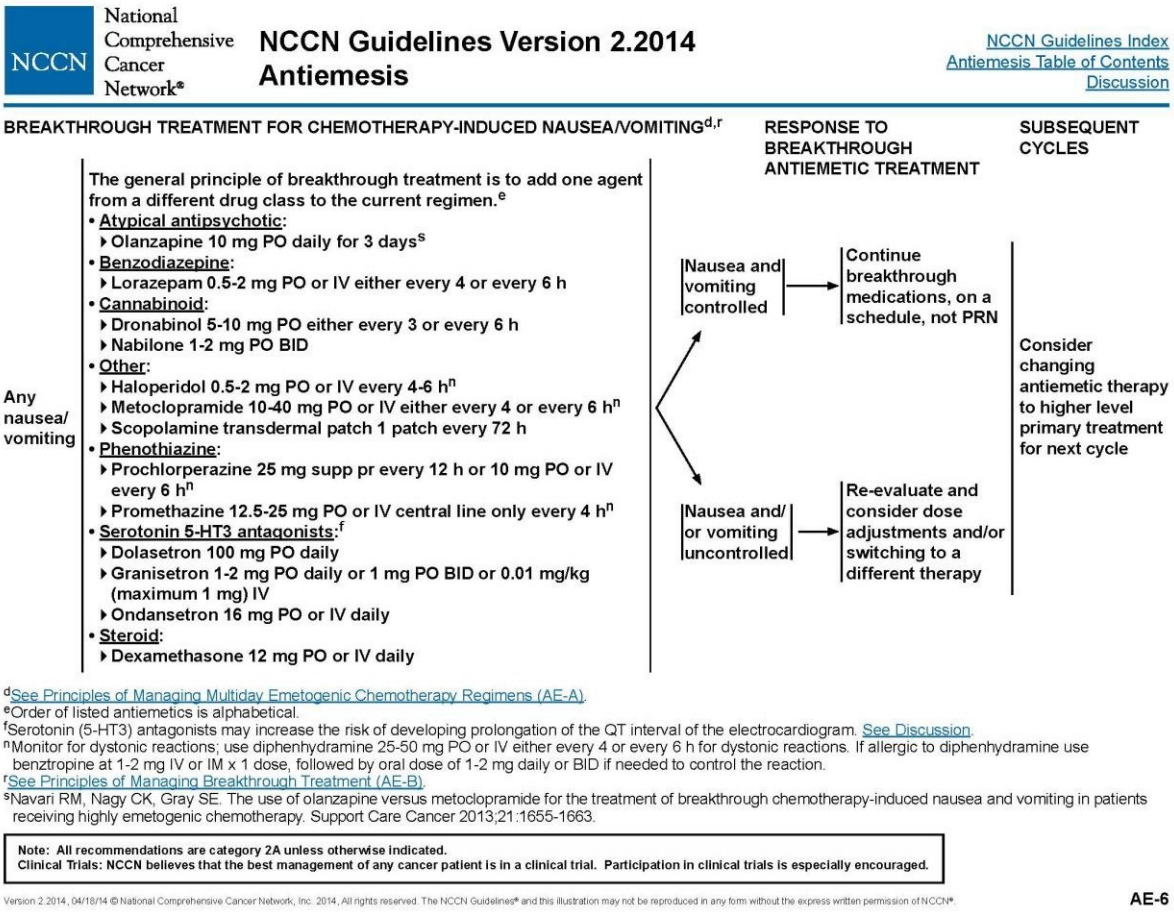
→ See Breakthrough Treatment (AE-6)

[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.

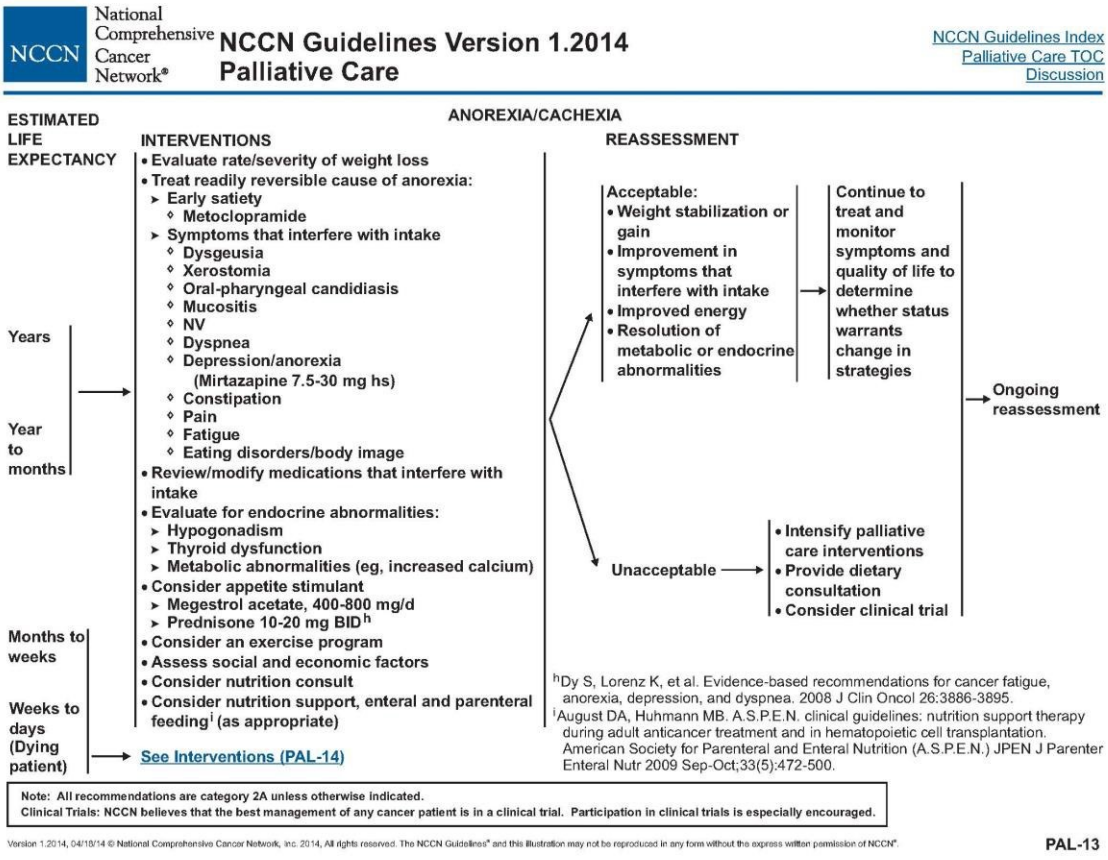
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

AE-2





20.6 Appendix 6: NCCN Clinical Practice Guidelines in Oncology: Anorexia/Cachexia



20.7 Appendix 7: Sample Collection and Shipping Summary

Karyopharm

Karyopharm will perform functional assays to assess NFkB and WNT pathway signaling and cytokine levels. blood and bone marrow samples will be delivered to the MSKCC HOTB for centrifugation, aliquotting and storage. Details are provided in the Karyopharm laboratory manual.

Sample Collected:

No.	TIME POINT	TOTAL VOLUME OF BLOOD (mL)	PDn		
			Cytokines 1 tube x 2 ml EDTA	Leukocytes 3 PAXgene Tubes x 2.5 ml	Bone Marrow* 2 aliquots x 1x10^{6}cells
	Baseline (Day -21 to -1)				x
	Cycle 1, Day 1				
1	Pre-dose (within 10 min before dosing)	9.5	2 ml	3 x 2.5ml	
2	4 hr (±20 min) post dose	9.5	2 ml	3 x 2.5ml	
3	8 hr (±20 min) post dose	9.5	2 ml	3 x 2.5ml	
	Cycle 1, Day 14				
4	Pre-dose (within 10 min before dosing)				x
	Cycle 1, Day 21				
5	Pre-dose (within 10 min before dosing)	9.5	2 ml	3 x 2.5ml	x
6	4 hr (±20 min) post dose	9.5	2 ml	3 x 2.5ml	
	Cycle 2, Day 21				
7	Pre-dose (within 10 min before dosing)	9.5	2 ml	3 x 2.5ml	x
8	4 hr (±20 min) post dose	9.5	2 ml	3 x 2.5ml	
	Cycle 4, Day 21				
9	Pre-dose (within 10 min before dosing)	9.5	2 ml	3 x 2.5ml	x
10	4 hr (±20 min) post dose	9.5	2ml	3 x 2.5ml	
11	**Off study**				x

*Not included in total volume of blood and may be collected any time pre-dose (not necessarilywithin 10 minutes before dosing).

Shipping Schedule:

Batched-shipped approximatelyonce each month on dry ice to Karyopharm via World Courier (account number 017300).at the following address:

Dr. Yosef Landesman
Karyopharm Therapeutics Inc.
75 Wells Avenue
Newton, MA 02459

Columbia

Dr. Gary Schwartz: blood and bone marrow aspirates will be shipped to Dr. Schwartz's laboratory at Columbia University for studies to assess the mechanism of selinexor. His laboratorywill perform the following analyses: Western blots for XPO1, p53, p21, PARP, and caspase. Specimens will be processed using ficoll-hypaque separation at the HOTB. Bone marrow and blood mononuclear cells will be viablycryopreserved (in DMSO) and stored for shipping.

Sample Collected: two 7mL EDTA tubes

No.	TIME POINT
1	**Baseline (Day -21 to -1)**
2	**Cycle 1, Day 7 (±1 day)**
3	**Cycle 1, Day 14 (±3 day)**
4	**Cycle 1, Day 21 (±1 day)**
5	**Cycle 2, Day 21 (±1 day)**
6	**Cycle 4, Day 21 (±1 day)**
7	**End of Study**

Shipping Schedule:

Batch-shipped approximatelyonce each month on dry ice to the laboratory of Dr. Schwatrz at Columbia Universityc/o Shyamprasad Deraje Vasudeva via FedEx (account number 2346-5338-5).at the following address:

Dr. Gary Schwartz c/o Shyamprasad Deraje Vasudeva
Columbia University
1130 Saint Nicholas Ave
ICRC Room 207, Schwartz Lab
New York, NY 10032

MSKCC Surgical Pathology

Dr. Chiu will direct the processing of bone marrow immunohistochemical (IHC) stains, which will be performed by the Pathology Core Laboratory at MSKCC to assess nuclear localization of beta catenin and p65, thereby assessing for evidence of WNT and NF-kB pathway signaling activation, respectively. Bone marrow specimens will be processed routinely for response assessment at the designated time points as per the protocol. Specimens will be directed to Dr. April Chiu. Extra sections will be obtained under the direction of Dr. April Chiu, and the Core Laboratory will perform.IHC for nuclear beta catenin and p65 using standard IHC techniques.

Sample Collected: Bone Marrow Immunohistochemical Stains

No.	TIME POINT
1	**Baseline (Day -21 to -1)**
2	**Cycle 1, Day 14 (±3 day)**
3	**Cycle 1, Day 21 (±1 day)**
4	**Cycle 2, Day 21 (±1 day)**
5	**Cycle 4, Day 21 (±1 day)**
6	**End of Study**

MD Anderson Cancer Center

Dr. Andreef will assess nuclear and cytoplasmic p53 localization on unstained bone marrow aspirate smears. Bone marrow aspirate slides are prepared at the time of the bone marrow procedure as per standard routine. No processing is required. These slides will be delivered to Dr. Klimek and will be stored at room temperature until they are shipped.

Sample Collected: Unstained Bone Marrow Aspirate Smears

No.	TIME POINT
1	**Baseline (Day -21 to -1)**
2	**Cycle 1, Day 14 (±3 day)**
3	**Cycle 1, Day 21 (±1 day)**
4	**Cycle 2, Day 21 (±1 day)**
5	**Cycle 4, Day 21 (±1 day)**
6	**End of Study**

Shipping Schedule:

Batch-shipped by UPS approximately every three months at ambient temperature in plastic slide carriers to Dr. Andreef. Specimens will be sent to the attention of Teresa Mcqueen (using Fedex accout # 136495291) at the following address:

Teresa Mcqueen
MD Anderson Cancer Center
6767 Bertner Ave.
T6.3948
Houston Tx 77030