Karyopharm Expanded Access Program for the Treatment of Patients with Multiple Myeloma Patients with SVd: Selinexor (KPT-330) plus Velcade (Bortezomib) and Dexamethasone

Product Name: Selinexor

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Confidentiality Statement

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1 Objective & Rationale

The treatment of Multiple Myeloma (MM) has improved in the last 20 years due to the use of high-dose chemotherapy (i.e., alkylating agents) and autologous stem cell transplantation, the introduction of immunomodulatory agents, such as thalidomide, lenalidomide, and pomalidomide, and the proteasome inhibitors, bortezomib and carfilzomib. However, despite the increased effectiveness of these agents, most patients develop highly resistant MM and succumb to the disease. With over 12,500 deaths from MM expected in the USA in 2016, there remains a high unmet medical need to develop anti-MM agents with novel mechanisms.

The Karyopharm Expanded Access Program (KEAP) aims to provide selinexor to patients with MM who have exhausted all available treatment options and are ineligible for any open clinical trials with selinexor. Selinexor will be made available as long as the patient is deriving benefit or until such time that it is commercially available in the patient's country, or Karyopharm, the drug manufacturer, chooses to discontinue the KEAP program or the patient withdraws consent.

This Treatment Plan provides guidance for the treatment of patients with Multiple Myeloma with selinexor plus Velcade (bortezomib) and dexamethasone (SVd). Karyopharm will only be providing selinexor as part of KEAP and will not be responsible for the provision of Velcade (bortezomib), dexamethasone or other supportive care medications.

2 Overview

Multiple myeloma (MM) is the second most common hematological malignancy (after non-Hodgkin lymphoma), representing 1% of all cancers and 2% of all cancer deaths, with approximately 32,270 new MM cases and 12,830 deaths due to MM anticipated in 2020 in the United States (US) alone (*American Cancer Society 2020*). Despite the approval of a variety of novel agents in recent years, MM still remains a largely incurable and a fatal disease, and nearly all patients inevitably relapse following therapy and develop refractory disease. The median survival in MM is approximately 6 years[1], and the median 5 year-survival is 53.9% (*SEER 2010-2016*). Thus, new treatment modalities are needed to improve both short- and long-term outcomes.

Although the cause of MM is unknown, a number of mutated genes have been found with significant frequency in patients with MM. These include mutations in NRAS, KRAS, TP53, and BRAF, which are well-known oncogenic drivers for other cancers[2], and mutations in many genes associated with NFκB activation[3]. Fifty percent of patients with MM harbor mutations in the immunoglobulin (Ig) heavy-chain locus on chromosome 14q32, partial or complete loss of chromosome 13, and partial loss of chromosome 17[4]. Additional risk factors such as age (≥65 years), male sex, and having family members affected by MM make some patients more susceptible to the disease.

Treatment of MM with selinexor plus Velcade (bortezomib) and dexamethasone has been studied in the clinical trials KCP-330-017, STOMP (#NCT02343042) and KCP-330-023, BOSTON (#NCT03110562).

3 Selinexor

Selinexor is an oral, first in class, slowly reversible, potent and Selective Inhibitor of Nuclear Export (SINE) compound that specifically blocks Exportin 1 (XPO1). Data indicate that Selinexor restores many of the tumor suppressor proteins (TSP) and growth regulatory (GRP) proteins to the nucleus where they can carry out their normal functions[5]. Data show that it is selectively cytotoxic for tumor cells, both *in vitro* and *in vivo*[5,6] While all cell types exposed to SINE compounds *in vitro* undergo G1/S ± G2/M cell cycle arrest, this arrest leads to apoptosis in cancer but not in normal cells. Data shows that normal cells treated with selinexor and other SINE compounds remain in transient, reversible cell cycle arrest until the export block is relieved[7-9]. Data indicate that 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[10]. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells and their functions are largely spared.

XPO1 inhibition can restore the activity of multiple tumor suppressor proteins (TSP) including p53, Rb, and p27; and reduce cyclins and Akt. Selinexor is an oral XPO1 inhibitor that shows potent anti-myeloma activity in preclinical models and clinical activity in early phase trials (STOMP KCP-330-017) in combination with Velcade (bortezomib). Selinexor in combination with Velcade (bortezomib) is currently in phase 3 clinical trials (BOSTON KCP-330-023).

4 Drug Supply

Karyopharm will supply selinexor tablets for oral use through their Expanded Access Program provider, Caligor Coghlan. Karyopharm will not supply any other medication or procedures as a part of this treatment. Selinexor will be provided as 20 mg strength tablets in 12 count blister packs. Tablets will be stored according to the label conditions: Do not store above 30°C (86°F). Do not freeze.

5 Patient Eligibility Criteria

The patient will be required to sign an informed consent regarding the use of selinexor as an unlicensed investigational medical product (IMP) which includes side effect information from the most recent copy of the Investigator Brochure (IB). The ICF will be approved according to local and regional laws by the appropriate Institutional Review Board (IRB) / Ethics Committee (EC). Approval will be obtained prior to initiating treatment, unless documented emergency request procedures allowing for expanded access are provided.

Inclusion criteria:

- Patient has relapsed/refractory multiple myeloma
- Aged 18 years and older
- Patient able to provide written, informed consent to participate in and follow the KEAP Treatment Plan
- Negative hCG pregnancy test for premenopausal women of reproductive capacity (those who are biologically capable of having children) and women less than 12 months after menopause. Women are considered post-menopausal if they are ≥ 12 months without menses, in the

absence of endocrine or anti-endocrine therapies.

It is recommended that:

Women of child-bearing potential agree and commit to use of a highly effective non- hormonal method of contraception from the time of informed consent until 28 days after the last dose of selinexor.

Men without confirmed vasectomy and their female partners of child-bearing potential should agree and commit to use a highly effective barrier method of contraception (i.e., any of the above methods of hormonal contraception associated with inhibition of ovulation) while receiving selinexor and for 3 months after the last selinexor dose, or consent to total sexual abstinence (abstinence must occur from enrollment and continue for 3 months after the last selinexor dose).

Exclusion criteria:

- Eligibility with reasonable access to a clinical site for open selinexor clinical trial within patient's country of residence
- Known hypersensitivity to selinexor or any excipients.
- Women who are pregnant, are planning on becoming pregnant, or are breast-feeding.
- Patient receiving any other investigational agent.
- Any concurrent uncontrolled and active medical condition or disease (e.g., uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, etc.).
- Known intolerance, hypersensitivity, or contraindication to glucocorticoids.
- Active graft versus host disease (after allogeneic stem cell transplantation).
- Active, unstable cardiovascular function:
  - *Symptomatic ischemia, or uncontrolled clinically significant conduction abnormalities (e.g., patients with ventricular tachycardia on anti-arrhythmics)*
  - *Congestive heart failure of New York Heart Association Class ≥ 3 or known left ventricular ejection fraction < 40%, or*
  - *Myocardial infarction within 3 months prior to C1D1.*
- Patients with symptoms of Greater than Grade 2 peripheral neuropathy or Grade ≥2 peripheral neuropathy with pain at baseline
- Significant renal impairment with ongoing dialysis treatment (*Waiver can be granted after discussion and approval from Karyopharm Chief Medical Officer*)
- Active gastrointestinal dysfunction interfering with the patient's ability to swallow tablets, or any active gastrointestinal dysfunction that could, in the treating physician's opinion, interfere with absorption of treatment.
- Any active, serious psychiatric, medical, or other conditions/situations which, in the treating physician's opinion, could compromise the patient's safety.

6 Dosing Schedule

Selinexor should be taken orally and swallowed whole with at least 120 mL (4 ounces) of fluids (water, juice, etc.). Selinexor tablets are coated and should not be crushed to avoid skin contact with the powder within.

Treatment plan and dose modification schedule are based on the KCP -330 017 trial (STOMP). The STOMP study was a phase 1 dose escalation study with several arms evaluating selinexor in combination with lenalidomide, pomalidomide, bortezomib and daratumumab in patients with RRMM. In the arm with selinexor/bortezomib/dexamethasone (SVD) the RP2D supported the below treatment regimen. The ORR in patients with bortezomib naïve disease was 84% and in 43% in patients with disease refractory bortezomib refractory.

- *Selinexor will be given as a fixed oral 100 mg dose (five 20 mg tablets) on Days 1, 8, 15, 22, and 29 of each 35-day cycle.*
- *Bortezomib will be given at a dose of 1.3 mg/m^2 SC on Days 1, 8, 15, and 22 of each 35- day cycle.*
- *Dexamethasone will be given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.*

In general, where possible, each treatment (selinexor, bortezomib, dexamethasone) should be given at least 1 to 2 hours apart. Dexamethasone should be administered at least 1 hour before selinexor and bortezomib.

Selinexor doses should not be administered less than 36 hours apart and no more than 2 doses in a 7 day period. Do not exceed 70 mg/m^2 per selinexor dose or 100 mg of selinexor in a single day for any patient.

7 Recommended Dose Modifications and Supportive Care for Management of Adverse Drug Reactions

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the expanded access treatment. The criteria for suggested dose modifications for toxicities considered at least possibly related to the expanded access medication treatments, as well as recommended supportive care, are outlined below.

Table 1: Prespecified Dose/Schedule Modifications for Adverse Events Related to selinexor

Selinexor Dose Level	Total Weekly Selinexor Dose	Selinexor Dose Schedule
Dose Level 0 (Starting Level)	100 mg	100 mg QW
Dose Level -1	80 mg	80 mg QW
Dose Level -2	60 mg	60 mg QW
Dose Level -3	40 mg	40 mg QW

Abbreviations: AEs = adverse events; BIW = twice weekly; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; QW = once weekly.

In order to minimize nausea, unless contraindicated, all patients should receive serotonin receptor subtype (5-HT3) antagonists starting on Day 1, before the first dose of treatment and continued, as needed, 2-3 times daily (e.g., ondansetron 4-8 mg q8h, day of ±day after selinexor). In those patients in whom a 5-HT3 antagonist is contraindicated or not sufficient, use of olanzapine (2.5- 5.0 mg po qAM) is recommended based on Investigator experience during Phase 1 selinexor studies. Additional options can be found in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO) for antiemesis and anorexia/cachexia (palliative care).

For cases appetite/weight loss consider olanzapine (2.5-5.0 mg po qAM). Other alternatives for appetite simulation include megestrol acetate (400 mg po qd), mirtazapine (15 mg po qPM). Mirtazapine should be given cautiously to patients with fatigue and given at night.

In cases of fatigue, check for underlying causes (dehydration, anemia, reduced appetite) and optimize hydration and caloric intake. Low dose stimulant such as methylphenidate also known as Ritalin (5-20 mg po qAM only; do not give >1 dose/day) or low dose dexamethasone (8-20 mg on selinexor dosing days) can help. Also consider decreasing mirtazapine dose (if applicable) and/or reduce other agents which cause fatigue.

Additional options can be found in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO) for antiemesis and anorexia/cachexia (palliative care).

Table 2 contains supportive care and dose adjustment guidelines for AEs related to selinexor. After consultation with the treating physician, selinexor dosing may be maintained for all AEs that are NOT related to selinexor.

For all selinexor-related AEs, if the prescribed dose reductions/interruptions in Table 2 result in a stabilization of ≥ 4 weeks, a re-escalation may be considered.

The possibility of overlapping toxicities with bortezomib and/or dexamethasone should be considered and it is strongly recommended that the dose is reduced or interrupted for 1 drug at a time.

Table 2: Supportive Care and Dose Adjustment Guidelines for AEs Related to selinexor

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Fatigue	
Grade 1 or Grade 2 lasting ≤ 7 days	Maintain dose. Check for underlying causes (dehydration, anemia, reduced appetite) and optimize hydration and caloric intake. If found to be anemic, consider transfusing for hemoglobin < 8 g/dL. Patients with significant fatigue after several doses of selinexor may have an ongoing antitumor response. If fatigue is significant, consider assessment of tumor response as part of the patient's evaluation.
Grade 2 lasting > 7 days or Grade ≥ 3	Rule out other causes. If found to be anemic, consider transfusing for hemoglobin < 8 g/dL. Interrupt selinexor dosing until resolved to Grade 1 or baseline. Low dose stimulant such as methylphenidate also known as Ritalin (5-20 mg po qAM only; do not give >1 dose/day) or low dose dexamethasone (8-20 mg on selinexor dosing days) can help. Also consider decreasing mirtazapine dose (if applicable) and/or reduce other agents which cause fatigue. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level. Patients with significant fatigue after several doses of selinexor may have an ongoing antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Anorexia or Weight Loss	
Grade 1 anorexia or weight loss Grade 2 anorexia	Maintain dose. Rule out other causes. Consider a repeat nutritional consultation and use nutritional supplements (e.g., Ensure®, Boost®, etc.). Consider olanzapine (2.5-5.0 mg po qAM)Other alternatives for appetite simulation include megestrol acetate (400 mg po qd), mirtazapine (15 mg po qPM), or low dose dexamethasone (8-20 mg on selinexor dosing days). Mirtazapine should be given cautiously to patients with fatigue and given at night.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Grade 2 weight loss Grade ≥ 3 anorexia and weight loss	Rule out other causes. Consider a repeat nutritional consultation and use nutritional supplements (e.g., Ensure®, Boost®, etc.). Olanzapine (2.5-5.0 mg po qAM) is an effective appetite stimulant for appetite loss due to selinexor. Other alternatives for appetite simulation include megestrol acetate (400 mg po qd), mirtazapine (15 mg po qPM), or low dose dexamethasone (8-20 mg on selinexor dosing days). Mirtazapine should be given cautiously to patients with fatigue and given at night. Interrupt selinexor dosing until anorexia or weight loss improves to Grade 1 or baseline and weight stabilizes. Reduce selinexor by 1 dose level.
Nausea, Acute	
Grade 1 or 2 (If intolerable or persistent Grade 2 not responsive to supportive care, follow guidelines for Grade 3)	Maintain dose. Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists. In those patients in whom a 5-HT3 antagonist is contraindicated or not sufficient, use of olanzapine (2.5-5.0 mg po qAM) is recommended based on Investigator experience during Phase 1 selinexor studies. Additional options can be found in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO) for antiemesis and anorexia/cachexia (palliative care).
Grade 3	Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists In those patients in whom a 5-HT3 antagonist is contraindicated or not sufficient, use of olanzapine (2.5-5.0 mg po qAM) is recommended based on Investigator experience during Phase 1 selinexor studies. Additional options can be found in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO) for antiemesis and anorexia/cachexia (palliative care). Interrupt selinexor dosing until resolved to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level.
Hyponatremia	
Grade 1 (sodium levels < Normal to 130 mmol/L)	Maintain dose. Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). Treat hyponatremia per institutional guidelines including dietary review. Consider addition of salt tablets to patient's diet.
Grade 3 with sodium levels 120 to 129 mmol/L without symptoms	Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). If (corrected) sodium is Grade ≤ 3 and continues to be asymptomatic, then patient may continue current dosing provided that IV saline and/or salt tablets are provided. If Grade 3 is persistent or worsens or does not respond to treatment, interrupt selinexor dosing until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Grade 3 with sodium levels 120 to 129 mmol/L with symptoms or Grade 4 (< 120 mmol/L)	Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). Interrupt selinexor dosing until resolved to Grade 1 or baseline and without symptoms. Reduce selinexor by 1 dose level.
Diarrhea	
Grade 1	Maintain dose. Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals.
Grade 2	Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals. Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level.
Grade 3 or 4	Interrupt selinexor dosing until resolved to Grade 1 or baseline and patient is clinically stable. Reduce selinexor dose by 1 dose level.
Thrombocytopenia	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 without bleeding	Rule out other causes including drug effects. For first occurrence: continue dosing without interruption, however, reduce selinexor by 1 dose level. **However, for patients with thrombocytopenia due to packed marrow, disease burden, or platelet that start with <75,000, dosing modification should be per physician, and guidance below can be adapted.** For ≥ second occurrence: interrupt selinexor and check platelet counts weekly until recovery to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level. If the occurrence falls on Day 1 of a cycle, delay start of the cycle and check platelet counts weekly until recovery to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level when resuming. In cases where there is significant disease involvement in the bone marrow (i.e., ≥ 50% marrow involvement) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the treating physician may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines
Grade 4 without bleeding	Rule out other causes including drug effects. Interrupt selinexor until recovery to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level. If the occurrence falls on Day 1 of a cycle, delay start of the cycle and check platelet counts weekly until recovery to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level when resuming. In cases where there is significant disease involvement in the bone marrow (i.e., ≥ 50% marrow involvement) or pre-existing compromised marrow function (e.g., due to prior marrow-toxic therapy), the treating physician may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored.
Grade ≥ 3 with bleeding	Interrupt selinexor dosing and check platelet counts weekly until the bleeding has stopped, patient is clinically stable, and the platelets have recovered to Grade 2 or baseline. When resuming selinexor, reduce by 1 dose level. If the occurrence falls on Day 1 of a cycle, delay start of the cycle and check platelet counts weekly until the bleeding has stopped, patient is clinically stable, and the platelets have recovered to Grade 2 or baseline and reduce selinexor by 1 dose level when resuming.
Neutropenia	
Grade 3 or 4 Neutropenia with fever (febrile neutropenia) or without fever	Institute colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines. Interrupt selinexor and check neutrophils weekly until recovery to Grade ≤ 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reduce selinexor by 1 dose level when resuming. If the occurrence falls on Day 1 of a cycle, delay start of a cycle and check neutrophils weekly until recovery to Grade ≤ 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reduce selinexor by 1 dose level when resuming.
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for hemoglobin < 8 g/dL. If possible, maintain selinexor dose as long as patient is clinically stable, but if dose reduction or interruption is desired, consult with the treating physician.	
Other selinexor-related adverse events	
Grade 1 or 2	Rule out other causes. Maintain dose. Initiate treatment and/or standard supportive care per institutional guidelines.
Grade 3 or 4	Rule out other causes. Interrupt selinexor until recovery to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level. Isolated values of Grade ≥ 3 alkaline phosphatase do NOT require dose interruption. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.
All dose modifications should be based on the worst preceding toxicity. Note: It is strongly encouraged that the dose is reduced or interrupted 1 drug at a time for those AEs that are thought to have multifactorial causes.	

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines

Abbreviations: IV: intravenous; NCCN: National Comprehensive Cancer Network; q8h: every 8 hours; qd: once daily; qAM: every morning; qPM: every afternoon or evening; QW: once per week; BIW: twice weekly; po: oral; SC: subcutaneous: TLS: tumor lysis syndrome; 5-HT3 = 5-hydroxytryptamine; AE = adverse event.

Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled or suspected infections should have treatment withheld until the infection has clinically resolved and/or the patient is clinically stable. When ready to resume dosing, treatment may continue at the original dose. Patients may continue on antibiotics for prolonged periods while re-initiating their treatment.

Interruption of selinexor

A patient may withdraw from the treatment plan at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

*The Investigator **may** remove a patient from study treatment for any of the following reasons*:

- Unacceptable AEs or toxicity that cannot be managed by supportive care
- Significant deviations from inclusion/exclusion criteria
- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk

*The Investigator **must** remove a patient from treatment for any of the following reasons*:

- Patient withdraws consent to continue study treatment.
- Progression of renal dysfunction requiring dialysis.
- Grade 4 AEs related to selinexor.

If AE requires interruption of selinexor and the selinexor dose interruption lasts for > 28 days, the treating physician should notify Karyopharm's representative (Caligor Coglin). After consulting with Karyopharm medical personnel, treating physician should decide if the patient should continue with the expanded access treatment or discontinue. Please refer to section 9.0 regarding adverse event reporting.

Conditions Not Requiring Selinexor Dose Reduction

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

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

- Isolated values of Grade ≥ 3 alkaline phosphatase. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.

Dose Modifications for Overlapping Toxicities

Thrombocytopenia and neutropenia are potential overlapping toxicities for selinexor with bortezomib. If a patient experiences drug-induced thrombocytopenia and/or neutropenia while receiving the combination, the treating physician should attempt to determine which drug may be responsible and treat appropriately, including dose modifications, as necessary. If, during the management of an AE for an individual patient receiving both selinexor and bortezomib, the treating physician suspects that bortezomib may be the cause of that event then the bortezomib dose may be adjusted during treatment according to the guidelines in the prescribing information for bortezomib (different local/regional trade names may be used). If the cause cannot be attributed to a single drug, it is strongly recommended that the dose is reduced or interrupted for 1 drug at a time. Please refer to Table 2 for AEs presumed to be related to selinexor.

The manufacturers of bortezomib have provided dose adjustment guidelines for managing Grade 3 to 4 thrombocytopenia and neutropenia that occur during treatment with bortezomib in the prescribing information.

Bortezomib Dose Modifications

For all bortezomib-related events, the bortezomib dose may be adjusted during treatment according to the guidelines in the prescribing information for bortezomib (different local/regional trade names may be used).

Dexamethasone Dose Modifications

The dose of dexamethasone should preferably remain constant throughout the treatment.

However, for patients with partial intolerance to dexamethasone, a dose reduction to a minimum dose of 10 to 12 mg dexamethasone BIW (i.e., a total minimum dose of 20 to 24 mg weekly) is permitted after a clear documentation of intolerance.

Management of Missed Doses

If a selinexor dose was missed, it can be taken for up to 24 hours after the scheduled treatment

Management of Vomited Doses

If a dose of selinexor is vomited within 1 hour of ingestion, it should be replaced. If vomiting occurs more than 1 hour after dosing, it should be considered a completed dose.

Treatment or Program Related Questions

For program or treatment related questions, contact the Caligor Coghlan by email at KEAP_Selinexor@calcog.com or via the web site https://selinexorkeap.caligorrx.com.
For AE's or SAE reporting questions, contact the Karyopharm pharmacovigilance team at pharmacovigilance@karyopharm.com.
A pregnancy occurring in a patient exposed to Karyopharm expanded access treatment must be reported to pharmacovigilance@karyopharm.com within 24 hours of first knowledge of its occurrence.
To contact Karyopharm KEAP team for any other issue or to speak with member of the Karyopharm expanded access medical team, please email KEAP@karyopharm.com.

8 Side effects of selinexor (KPT-330)

For a complete list of all treatment emergent side effects, consult the Investigators Brochure version 9

Very common side effects (≥10%) as of 31 March 2019:

Nausea	(65.1%)
Fatigue	(57.9%)
Thrombocytopenia	(52.1%)
Decreased appetite	(51.0%)
Anaemia	(42.3%)
Vomiting	(38.2%)
Diarrhoea	(36.0%)
Weight decreased	(33.9%)
Constipation	(28.4%)
Hyponatraemia	(26.5%)
Neutropenia	(24.7%)
Dyspnoea	(22.8%)
Dizziness	18.2%)
Dysgeusia	(17.3%)
Pyrexia	(17.2%)
Cough	(16.7%)
Vision blurred	(15.9%)
Leukopenia	(15.7%)
Abdominal pain	(14.6%)
Asthenia	(13.8%)
Hypokalaemia	(13.6%)
Oedema peripheral	(13.6%)
Dehydration	(12.7%)
Hyperglycaemia	(12.0%)
Headache	(11.9%)
Back pain	(11.5%)
Insomnia	(11.1%)
Pneumonia	(10.3%)

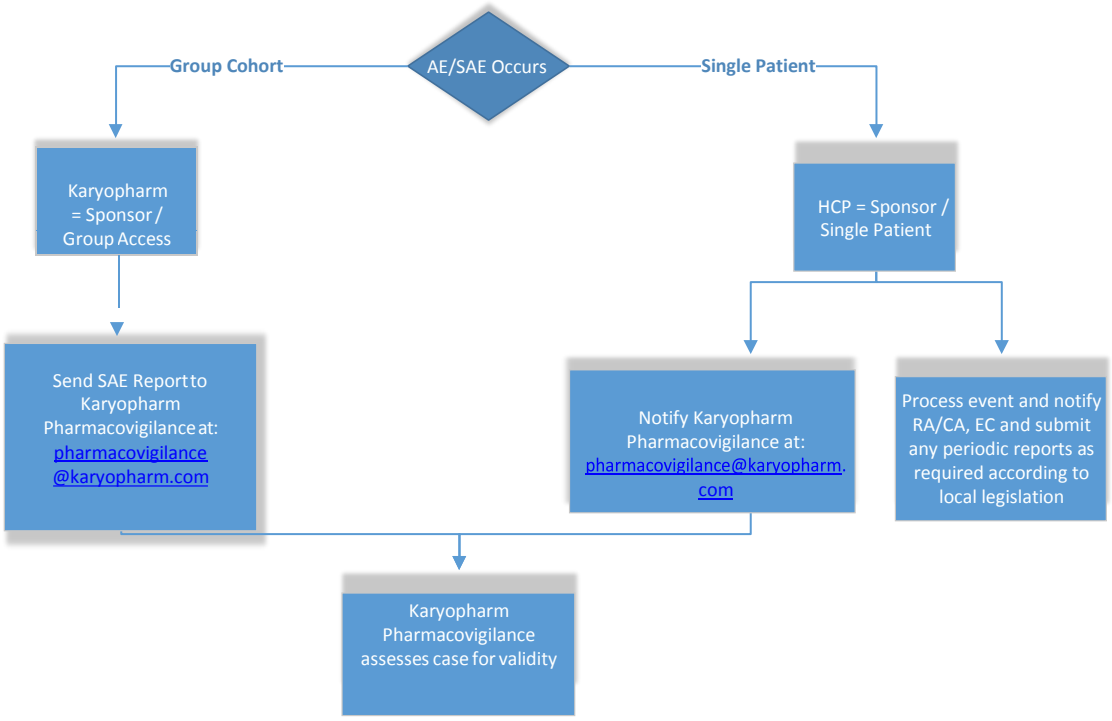
Most Commonly Reported (≥2%) Serious Adverse Events (SAE) **as of 31 March 2019**

Pneumonia	(7.6%)
Sepsis	(4.8%)
Febrile neutropenia	(4.3%)
Pyrexia	(2.9%)
Vomiting	(2.3%)
Anaemia	(2.1%)
Thrombocytopenia	(2.1%)
Dehydration	(2.0)
Fatigue	(2.0)

9 Safety and Safety Reporting

The treating physician will submit all Serious Adverse Events (SAE's) to Karyopharm within 24 hours by email (pharmacovigilance@karyopharm.com) in accordance with country specific Expanded Access regulations and laws. Karyopharm provides an SAE reporting form for this purpose.

Karyopharm Expanded Access Program Pharmacovigilance Process Flow



Adverse Events

In accordance with Good Clinical Practices, it is the responsibility of Institution to collect information regarding Adverse Events (AEs) and Serious Adverse Events (SAEs) independent of the causal relationship with the Drug (suspected or not) and of the nature of the AE (expected per the Drug Reference Safety Information or not).

Recording and Reporting Adverse Events

All AEs that begin or worsen after the patient has provided informed consent should be recorded by the Treating Physician, regardless of relationship to the expanded access treatment. AE monitoring should be continued for at least 30 days following the last dose of the selinexor treatment (i.e., through 30 days following last dose or until resolution or through the end of the treatment for events considered related to expanded access treatment by the Treating Physician).

Adverse Event Causality

The Treating Physician will assess the relationship of all AEs to the Drug and other expanded access treatment drugs, as outlined in Table 3 .

Table 3:Classification of Adverse Events by Causality

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

Reporting Serious Adverse Events

All Serious Adverse Events (SAE's) must be reported to Karyopharm within 24 hours by email (pharmacovigilance@karyopharm.com) in accordance with country specific Expanded Access regulations and laws. Treating Physicians are responsible as applicable for notifying their appropriate Health Authorities, Institutional Review Board or Local and Central Ethics Committees (EC) of all SAEs in accordance with local regulations. A copy of these notifications should be provided to Karyopharm along with reporting the SAE at pharmacovigilance@karyopharm.com.

Progression of the malignancy (including fatal outcomes) during the treatment or within the safety reporting period of treatment should not be reported as an SAE. Sudden and unexplained death should be reported as an SAE.

Selinexor Reference Safety Information

For the purposes of regulatory reporting and Suspected Unexpected Serious Adverse Reactions (SUSAR),

Table 4 identifies adverse reactions that can be considered 'expected' with the use of selinexor and therefore constitute the most current Reference Safety Information (RSI). Greater frequency and severity beyond what has been observed in clinical studies as of 31 March 2019 may alter medical opinion of expectedness for an adverse reaction.

Table 4: Serious Adverse Reactions for Selinexor Considered Expected for Safety Reporting Purposes as of 31 March 2019

SOC	**SARs**	**All SARs** **Number of Patients Exposed (N) = 2076** **n (%)**
Blood and lymphatic system disorders	Febrile neutropenia	52 (2.5)
	Thrombocytopenia	31 (1.5)

SOC	SARs	All SARs Number of Patients Exposed (N) = 2076 n (%)
	Anaemia	23 (1.1)
	Neutropenia	11 (0.5)
Eye disorders	Cataract	19 (0.9)
	Vision blurred	3 (0.1)
General disorders and administration site conditions	Fatigue	31 (1.5)
	Pyrexia	19 (0.9)
	Asthenia	12 (0.6)
Gastrointestinal disorders	Vomiting	40 (1.9)
	Nausea	35 (1.7)
	Diarrhoea	27 (1.3)
	Abdominal Pain	4 (0.2)
	Constipation	2 (0.1)
Infection and Infestation	Pneumonia	39 (1.9)
	Sepsis	27 (1.3)
	Lung infection	6 (0.3)
	Bacteraemia	3 (0.1)
	Bronchitis	3 (0.1)
	Upper respiratory tract infection	3 (0.1)
	Enterocolitis infectious	2 (0.1)
	Gastroenteritis	2 (0.1)
	Respiratory tract infection	2 (0.1)
	Rhinovirus infection	2 (0.1)
	Urinary tract infection	2 (0.1)

SOC	SARs	All SARs Number of Patients Exposed (N) = 2076 n (%)
Investigations	Weight decreased	5 (0.2)
Metabolism and nutrition disorders	Dehydration	33 (1.6)
	Hyponatraemia	25 (1.2)
	Decreased appetite	19 (0.9)
	Hypercreatininaemia	4 (0.2)
Nervous system disorders	Syncope	11 (0.5)
	Dizziness	4 (0.2)
Psychiatric disorders	Confusional state	12 (0.6)
	Mental Status Changes	2 (0.1)
Respiratory, thoracic and mediastinal disorders	Dyspnea	6 (0.3)
	Epistaxis	2 (0.1)

SAR: serious adverse reaction; SOC: system organ class.

In assessing expectedness, even if the suspected Serious Adverse Reaction (SAR) is included in the Reference Safety Information (RSI),

Table 4, it will be considered to be unexpected if there is a fatal outcome or it is assessed as life-threatening. Therefore, these fatal and life-threatening events must be reported in the required expedited manner to the health authorities and relevant ethics committees.

Pregnancy

A pregnancy occurring in a patient exposed to Karyopharm expanded access treatment must be reported to pharmacovigilance@karyopharm.com within 24 hours of first knowledge of its occurrence.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

Abuse, Misuse, Medication Errors, Overdose, and Occupational Exposure

Karyopharm Pharmacovigilance collects information regarding any abuse, misuse, medication errors, overdose, and occupational exposure to Karyopharm products. As such, all incidences of abuse, misuse, medication errors, overdose, and occupational exposure with Karyopharm products are required to be

reported to Karyopharm pharmacovigilance on an SAE report form emailed to pharmacovigilance@karyopharm.com, regardless of whether or not there is an associated AE or SAE. If the abuse, misuse, medication errors, overdose, and occupational exposure is associated with an SAE, the SAE report form must be submitted to pharmacovigilance@karyopharm.com within 24 hours of awareness.

10 References

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