BC Cancer Protocol Summary for the Treatment of Multiple Myeloma using Bortezomib, Selinexor, and Dexamethasone With or Without Cyclophosphamide

Protocol Code	*MYBSD*
Tumour Group	*Myeloma*
Contact Physicians	*Dr. Christopher Venner*

ELIGIBILITY:

Patients must have:

- Multiple myeloma, plasma cell leukemia, or systemic light chain amyloidosis
- Received at least one prior line of therapy,
- Sensitivity to bortezomib (which includes patients who relapse after maintenance bortezomib (MYBORMTN), or have not previously been exposed),
- For patients who have relapsed after a proteasome-inhibitor-containing regimen, they must have had:
  - At least partial response to most recent proteasome inhibitor, and
  - At least 6 months interval since last proteasome inhibitor
- For patients stable on bortezomib per MYBORREL or discontinued and have not progressed, may switch to MYBSD if all other eligibility criteria are met

EXCLUSIONS:

- Previous Grade 3 or higher bortezomib-related toxicity

CAUTIONS:

- Platelet count less than 30 x 10^9/L
- ANC less than 0.5 x 10^9/L may require giving filgrastim

TESTS:

- Baseline (required before first treatment): CBC & Diff, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): serum protein electrophoresis and serum free light chain levels, immunoglobulin panel (IgA, IgG, IgM), HCAb, HBsAg, HBsAb, HBcoreAb, beta-2 microglobulin
- If clinically indicated at baseline: ECG, phosphate, magnesium
- Days 8, 15, 22 of Cycle 1: CBC & Diff, creatinine, sodium, potassium, magnesium, calcium

- Every 4 weeks (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and serum free light chain levels
- Every 4 weeks (optional, results not mandatory but encouraged prior to each cycle): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM), beta-2 microglobulin
- Every 4 weeks: CBC & Diff, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
- Days 8, 15, 22 of Cycle 2 and onward: (Optional if pre-cycle cytopenias, hypercalcemia, hepatic or renal dysfunction, or steroid-induced diabetes a concern. Results do not have to be available to proceed with treatment. Provider to review results, no dose modifications indicated for mid-cycle bloodwork): CBC & Diff, creatinine, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, random glucose
- If clinically indicated: phosphate, magnesium
- If clinically indicated: HBV viral load (see protocol SCHBV)
- Cycle 1: weekly nursing assessment for signs and symptoms of side effects (in particular nausea and anorexia) from selinexor
- Cycle 2 onward: weekly nursing assessment for selinexor (optional)

PREMEDICATIONS:

Option A (first choice):

- Prior to each selinexor dose:
  - netupitant-palonosetron 300 mg-0.5 mg PO

Option B (if Option A not possible or not working):

- Prior to each selinexor dose:
  - aprepitant 125 mg PO, and
  - ondansetron 8 mg PO, and
- Following each selinexor dose:
  - aprepitant 80 mg PO daily for two days, and
  - ondansetron 8 mg PO up to TID prn nausea, and
  - Optional if additional antiemetic required: OLANZapine 2.5 mg PO in the evening of selinexor dose and the evening following each selinexor dose

SUPPORTIVE TREATMENT:

- Consider dietitian referral as clinically appropriate to ensure adequate oral hydration and optimize caloric intake during treatment
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with corticosteroid
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating bortezomib and selinexor. Patients should take valACYclovir 500 mg PO daily
- High risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
dexamethasone	20 mg* on Days 1, 2, 8, 9, 15, 16, 22, 23	PO, in the morning with food Take at least one hour prior to selinexor on selinexor days
selinexor	100 mg**† once weekly on Days 1, 8, 15, 22 ** at physician discretion (e.g., concern of gastrointestinal toxicity), may start with 60 mg or 80 mg once weekly and escalate to 100 mg once weekly if tolerated.	PO
bortezomib	1.3 mg/m^2 on Days 1, 8, 15	Subcutaneously (abdomen or thigh)***
cyclophosphamide (if using)	500 mg once weekly on Days 1, 8, 15, and 22 OR 50 mg once every 2 days	PO, in the morning may be preferred

* Dexamethasone dose may vary dependent on tolerability and co-morbidities. See also: Other options for steroid dosing, below

*** Back of the arm can also be considered as a third option, after abdomen or thigh

† Escalation of selinexor dose to 120 mg PO weekly (taken as 60 mg PO twice weekly on Days 1, 4, 8, 11, 15, 18, 22, 25) for cycle 3 onward is an option for patients who have not received at least partial response in first 2 cycles, are tolerating 100 mg weekly dose well, and not experiencing adverse events at time of dose escalation.

Repeat every 28 days until disease progression or unacceptable toxicity.

OTHER OPTIONS FOR STEROID DOSING:

- Can be used (but may result in lower efficacy). Dose should be adjusted based upon toxicity and patient tolerance. Some examples included below:

Option A: dexamethasone 20 mg PO once weekly (or dexamethasone 4 to 40 mg PO once weekly based on toxicity and patient tolerance)
Option B: predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance. (e.g. predniSONE 10 to 100 mg PO once weekly)
Option C: No dexamethasone or predniSONE. High-dose steroids may need to be avoided in certain patients who are intolerant or have difficulty with side-effects. It is expected that the response will be inferior than without high-dose steroids. High-dose steroids may be added for non-response.

DOSE MODIFICATIONS:

- **Bortezomib dose levels:**

Dose level 0	Dose level -1	Dose level -2	Dose level -3
1.3 mg/m^2	1 mg/m^2	0.7 mg/m^2	0.5 mg/m^2

- **Selinexor dose levels:**

Dose Level +1	Dose level 0	Dose level -1	Dose level -2	Dose level -3
60 mg twice weekly	100 mg once weekly	80 mg once weekly	60 mg once weekly	40 mg once weekly

1. Hematological: for bortezomib (based on pre-cycle labwork):

ANC (x10^9/L) On Day 1		**Platelets (x10^9/L)** On Day 1	**Bortezomib Dose**	**Cyclophosphamide Dose (if using)**
Greater than or equal to 0.5	and	Greater than or equal to 50	100%	100%
Greater than or equal to 0.5	and	30 to 49	Notify provider. Proceed but consider dose reduction by one dose level for low platelets.	Delay until recovery
Less than 0.5†	or	Less than 30*	May proceed but decrease by one dose level if felt to be treatment-related.	
Reoccurrence of less than 0.5†	or	Reoccurrence of less than 30*	For reoccurrence of ANC less than 0.5, may proceed but consider decrease by one dose level if felt to be treatment-related. Delay until platelets greater than or equal to 30, then consider decreasing by one dose level	

* follow hematology weekly and consider arrangements for transfusion support as required.
† Consider weekly filgrastim if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer.

Hematological: for selinexor (based on pre-cycle labwork):

ANC ($x10^9$/L) On Day 1		**Platelets ($x10^9$/L)** On Day 1	**Selinexor Dose**
Greater than 1.0	and	75 or greater	100%
0.5 to 1.0	or	25 to 74	▪ If no fever, and no signs of bleeding: proceed, but at one dose level lower ▪ If signs of bleeding: hold until bleeding has resolved, then restart at one dose level lower
Less than 0.5† Or Febrile neutropenia	or	Less than 25*	▪ Hold until ANC 0.5 or greater, and platelets 25 or greater, then restart at one dose level lower

* follow hematology weekly and consider arrangements for transfusion support as required.
† Consider weekly filgrastim if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer.

2. Nausea and vomiting:

Severity	**Management and Selinexor Dose**
Grade 1 or 2 nausea (oral intake decreased without significant weight loss, dehydration, or malnutrition) OR Grade 1 or 2 vomiting (5 or fewer episodes per day)	▪ Proceed at same selinexor dose ▪ Escalate anti-emetic treatment
Grade 3 nausea (inadequate oral caloric or fluid intake) OR Grade 3 or higher vomiting (6 or more episodes per day)	▪ Hold selinexor until nausea and/or vomiting Grade 2 or lower or baseline, then restart at one dose level lower ▪ Escalate anti-emetic treatment

3. Diarrhea:

Diarrhea grading system

Grade 1	Grade 2	Grade 3	Grade 4
Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated for less than 24hrs; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of greater than 7 stools per day over baseline; incontinence; IV fluids for greater than 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)

Supportive care for diarrhea:

- At first loose stool, start loperamide 4 mg stat, followed by 2 mg with every episode of diarrhea to a maximum of 16 mg daily
- If diarrhea free greater than 12 hours, stop loperamide. If new episode, retreat with loperamide
- Hydration and electrolyte replacement as clinically required

Dose of bortezomib and selinexor:

Severity of Diarrhea	Bortezomib Dose	Selinexor Dose
Grade 2	First occurrence: ▪ 100% per provider discretion Recurrent: ▪ Hold until less than 2 watery bowel movements per day, then restart at one dose level lower	First occurrence: ▪ 100% per provider discretion Recurrent: ▪ Hold until less than 2 watery bowel movements per day, then restart at one dose level lower
Grade 3 or higher	▪ Hold until less than 2 watery bowel movements per day, then restart at 80% of that used in the last course	▪ Hold until less than 2 watery bowel movements per day, then restart at one dose level lower

4. Weight loss and anorexia:

Severity	Management and Selinexor Dose
Weight loss of 10% to less than 20% OR Anorexia associated with significant weight loss or malnutrition	▪ Hold selinexor until weight returns to more than 90% of baseline, then restart at one dose level lower ▪ Treat supportively (nutritional support; dietitian referral suggested)

5. Hyponatremia:

Sodium Level (mmol/L)	Management and Selinexor Dose
Less than 130	▪ Hold until sodium 130 mmol/L or greater, then restart at one dose level lower ▪ Treat supportively (dietary modifications, and/or sodium supplementation; dietitian referral suggested) ▪ Monitor sodium levels as clinically indicated

6. Fatigue:

Severity	Management and Selinexor Dose
Grade 2 lasting greater than 7 days (not relieved by rest; limiting instrumental ADL) OR Grade 3 (not relieved by rest, limiting self care ADL)	▪ Hold selinexor until Grade 1 (fatigue relieved by rest) or baseline, then restart at same selinexor dose ▪ If recurrent, hold until Grade 1 or baseline, then restart at one dose level lower

7. Ocular toxicity:

- Hold selinexor for any changes in vision until assessment by appropriate specialist. Suggested management below is for use after ophthalmologic evaluation

Toxicity and Severity	Management and Selinexor Dose
Cataract (Grade 2 or higher)	▪ Proceed with selinexor, but at one dose level lower ▪ Ophthalmologic evaluation with ongoing monitoring for progression suggested ▪ If surgery, hold selinexor 24 hours prior to surgery and for 72 hours after surgery.
Other ocular toxicity, Grade 2	▪ Hold selinexor until resolution to Grade 1 or baseline, then restart at one dose level lower ▪ Ophthalmologic evaluation and supportive care as clinically indicated
Other ocular toxicity, Grade 3 or higher	▪ Discontinue selinexor ▪ Ophthalmologic evaluation

8. Peripheral Neuropathy:

Severity of Peripheral Neuropathy Signs and Symptoms	Bortezomib Dose
Grade 1 (paresthesia and/or loss of reflexes) without pain or loss of function	100%
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 1 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living	Delay until recovery. When resolved, reduce dose to 0.7 mg/m^2 weekly
Grade 4 (permanent sensory loss that interferes with function)	Discontinue

9. Hepatic Impairment:

<table>
<tr><th></th><th>Bilirubin</th><th>ALT or AST</th><th>Bortezomib Dose</th><th>Selinexor</th><th>Cyclophosphamide Dose (if using)</th></tr>
<tr><td rowspan="2">Mild</td><td>less than or equal to 1 x upper limit of normal</td><td>greater than the upper limit of normal</td><td>100%</td><td>100%</td><td rowspan="4">100%</td></tr>
<tr><td>greater than 1 to 1.5 x upper limit of normal</td><td>Any</td><td>100%</td><td>100%</td></tr>
<tr><td>Moderate</td><td>greater than 1.5 to 3 x upper limit of normal</td><td>Any</td><td rowspan="2">▪ Reduce dose to 0.7 mg/m^2 in the first cycle.
▪ Consider dose escalation to 1 mg/m^2 <u>*or*</u> further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.</td><td rowspan="2">▪ Limited data
▪ Proceed per prescriber discretion</td></tr>
<tr><td>Severe</td><td>greater than 3 x upper limit of normal</td><td>Any</td></tr>
</table>

10. Renal Dysfunction:

Bortezomib and selinexor:

- No dose reduction is necessary for renal dysfunction.
- For patients on hemodialysis, give doses after dialysis.

Cyclophosphamide:

- Dose reduction is necessary per table, below. Physician may consider giving full dose of cyclophosphamide irrespective of renal function if deemed to be of benefit.
- For patients on hemodialysis, give dose after dialysis.

Creatinine clearance (mL/min)	Cyclophosphamide Dose
Greater than or equal to 10	100 %
Less than 10	75 %

PRECAUTIONS:

1. **Hematologic toxicity:** treatment with selinexor can result in life-threatening bone marrow suppression; Grade 3 or 4 thrombocytopenia occurred in 43% of patients and Grade 3 or 4 neutropenia in 12% of patients in one study. Monitor patients for signs of bleeding and infection closely. Dose interruption and reduction may be required, see dose modifications, above.
2. **Gastrointestinal side effects** including nausea, vomiting, anorexia and diarrhea can be severe during treatment with selinexor. Provide patient with antiemetics both for prophylaxis and treatment of nausea. Patients should receive instruction regarding the use of antiemetics and loperamide prior to treatment initiation. See dose modifications, above.

   It is recommended that for at least the first 2 cycles of treatment patients monitor their weight daily and keep a journal that can be submitted to the physician at the next appointment.
3. **Hyponatremia** can occur during treatment with selinexor, sometimes associated with gastrointestinal toxicity, and can be life-threatening. Sodium may appear lower in the context of elevated glucose or high serum paraprotein levels. Correct sodium level for high paraprotein level or concurrent hyperglycemia if serum glucose is greater than 8.3 mmol/L.
4. Treatment with selinexor can result in **serious infections**, with Grade 3 or higher infections reported in up to one-third of patients. Most infections were not associated with Grade 3 or higher neutropenia. Monitor for signs of infection and initiate treatment immediately.
5. **Neurologic toxicities** can occur during treatment with selinexor. Monitor patient for symptoms including confusion, dizziness, fainting, balance problems, hallucinations, delirium, changes in mood and behavior.

6. **Ocular toxicities** including new onset or exacerbation of cataract are reported during treatment with selinexor. Baseline optometrist or ophthalmology consult prior to treatment initiation should be considered. Ongoing monitoring during treatment with appropriate specialist recommended. Any changes in vision should prompt immediate referral for assessment. See dose modifications, above.
7. **Need for irradiated blood products:** Patients receiving an autotransplant require irradiated blood products from 7 days prior to collection to 3 months post transplant (6 months if total body irradiation conditioning) to eliminate the risk of potentially life-threatening transfusion-related graft-versus-host-disease. All other myeloma patients do not require irradiated blood products.
8. **Green tea avoidance:** Some of the components in green tea and preparations made from green tea block the activity of bortezomib in in vitro experiments. Green tea or preparations made from green tea should be avoided by patients taking bortezomib.
9. **Live vaccines:** Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
10. **Hepatitis B Reactivation:** See SCHBV protocol for more details.
11. **Peripheral Neuropathy:** occurs in 36–37% of patients receiving IV bortezomib with 8–14% resulting in grade 3–4 severity of symptoms. This is a common and often dose limiting side effect. Administration of bortezomib via the subcutaneous route instead of IV push significantly reduces the occurrence of peripheral neuropathy. Although reported during selinexor treatment, no additive toxicity was noted with addition of selinexor to bortezomib treatment.

Call Dr. Christopher Venner or tumour group delegate at 604-877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020 Nov 14;396(10262):1563-1573.
2. Richard S, Chari A, Delimpasi S, et al. Selinexor, bortezomib, and dexamethasone versus bortezomib and dexamethasone in previously treated multiple myeloma: Outcomes by cytogenetic risk. Am J Hematol. 2021 Sep 1;96(9):1120-1130.
3. Selinexor (Xpovio) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies 2022; 2(8): 1-28.
4. CADTH Reimbursement Review. Provisional Funding Algorithm. Multiple Myeloma. Nov 2022.