Regimen Monograph

A - Regimen Name

BORTDEXASELI Regimen

Bortezomib-Dexamethasone-Selinexor

Disease Site

Hematologic
Multiple Myeloma

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For treatment of multiple myeloma in patients who have received at least one prior therapy.

(Refer to NDFP form and EAP for detailed funding criteria.)

Supplementary Public Funding

bortezomib
New Drug Funding Program (Bortezomib - In Combination with Selinexor and Dexamethasone for Previously Treated Multiple Myeloma) (NDFP Website)

dexamethasone
ODB - General Benefit (dexamethasone)

selinexor
Exceptional Access Program (selinexor - In combination with bortezomib and dexamethasone for relapsed or refractory multiple myeloma) (EAP Website)

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B - Drug Regimen

bortezomib	1.3 mg /m²	IV / Subcut	Days 1, 8, 15, 22
dexamethasone	40 mg	PO	Days 1, 8, 15, 22, 29

In elderly patients, the dexamethasone dose should be reduced (i.e. to 20 mg once weekly).

selinexor	100 mg	PO	Days 1, 8, 15, 22, 29

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C - Cycle Frequency

REPEAT EVERY 35 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate*

*In the clinical trial, patients received a 5-HT3 receptor antagonist ± other antiemetics (e.g. olanzapine or NK1 RA) prior to and during treatment, and as needed after treatment.

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Other Supportive Care:

- Patients at risk of tumour lysis syndrome (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.
- Consider the use of antiviral prophylaxis against herpes zoster (shingles) during bortezomib therapy.
- Patients should maintain adequate fluid and caloric intake during treatment. Consider IV hydration for patients at risk of dehydration.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Dexamethasone doses may be reduced to improve tolerability, if dexamethasone-related adverse events persist despite supportive care measures.

Dose Level	Bortezomib Dose (mg/m^2)	Selinexor Dose (mg)
0	1.3	100
-1	1	80
-2	0.7	60
-3	Discontinue	40
-4	N/A	Discontinue

Dose Modifications for Bortezomib

Toxicity	Grade	Bortezomib Dose
ANC	< 0.5 x 10^9/L	Hold until recovery; restart at 1 dose level ↓.
Platelets	< 25 x 10^9/L	
Pneumonitis	Any	Hold and investigate; discontinue if confirmed.
PRES/ PML/ or dose-limiting toxicity at 0.7 mg/m^2	Any	Discontinue.
Other non-hematologic toxicity (except for neurotoxicity)	Grade ≥ 3	Hold until ≤ grade 1 or baseline; restart at 1 dose level ↓. Consider discontinuing for grade 4.
Peripheral neuropathy	Grade 1 (paresthesia, weakness and/or loss of reflexes)	If without pain or loss of function - No action is required. If with pain - Restart at 1 dose level ↓.
	Grade 2 (interfering with function but not with activities of daily living)	If without pain - Restart at 1 dose level ↓. If with pain - Hold until toxicity resolves; restart at 2 dose level ↓ (0.7mg/m^2).
	Grade 3 (interfering with activities of daily living)	Hold until toxicity resolves; restart at 2 dose level ↓ (0.7mg/m^2).
	Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis, and/or severe autonomic neuropathy)	Discontinue.

Dose Modifications for Selinexor

Toxicity	Grade	Selinexor Dose
Thrombocytopenia	Grade 2 or 3	Reduce by 1 dose level.
	Grade 2 or 3, with bleeding	Hold until bleeding resolves. Administer platelet transfusions as per institutional practice. Restart at 1 dose level ↓.
	Grade 4	Hold until Grade ≤ 2. Restart at 1 dose level ↓.
Neutropenia	Grade 3	Reduce by 1 dose level.
	Grade 4	Hold until Grade ≤ 2. Restart at 1 dose level ↓.
Febrile neutropenia	Any	Hold until ANC returns to ≥ 1 x 10^9/L. Restart at 1 dose level ↓.
Anemia	Grade 3	Reduce by 1 dose level. Administer blood transfusions and/or other treatments as per institutional practice.
	Grade 4	Hold until Grade ≤ 2. Administer blood transfusions and/or other treatments as per institutional practice. Restart at 1 dose level ↓.
Nausea/vomiting	Grade 3 or 4	Hold until Grade ≤ 2. Start additional anti-emetics. Restart at 1 dose level ↓.
Diarrhea	Grade 2	Hold until Grade ≤ 1. Restart at same dose. If recurs, hold until Grade ≤ 1. Restart at 1 dose level ↓.
	Grade 3 or 4	Hold until Grade ≤ 1. Restart at 1 dose level ↓.
Weight loss and anorexia	Grade 2 (10-19% decrease from baseline weight) OR Anorexia associated with significant weight loss or malnutrition	Hold until weight returns to > 90% of baseline. Restart at 1 dose level ↓.
Hyponatremia	Grade 4 (Na < 120 mmol/L)	Hold until Na ≥ 130. Restart at 1 dose level ↓.

Fatigue	Grade 2, lasting > 7 days OR Grade 3	Hold until Grade ≤ 1. Restart at same dose. If recurs, hold until Grade ≤ 1. Restart at 1 dose level ↓.
Any new or worsening visual disturbance		Refer to ophthalmologist for evaluation.
Ocular (excluding cataract)	Grade 2	Hold until Grade ≤ 1. Refer to ophthalmologist for evaluation. Restart at 1 dose level ↓.
	Grade 3 or 4	Discontinue. Refer to ophthalmologist for evaluation.
Cataract	Grade 2, 3 or 4	Reduce by 1 dose level. Refer to ophthalmologist for evaluation. If surgery is warranted, hold dose 24 hours pre- and for 72 hours post-surgery.
Other non-hematologic	Grade 3 or 4	Hold until Grade ≤ 2. Restart at 1 dose level ↓.

Hepatic Impairment

Use bortezomib with extreme caution in patients with hepatic impairment; closely monitor for toxicities.

Bilirubin		AST	Bortezomib Dosage	Selinexor Dosage
≤ ULN	and	> ULN	No change	No dose adjustment required.
>1 - 1.5 x ULN	and	Any		
>1.5 - 3 x ULN	and	Any	First cycle: ↓ to 0.7mg/m^2. Subsequent cycles: Consider ↑ dose to 1mg/m^2 or further ↓ dose to 0.5mg/m^2 based on patient tolerability.	Caution; limited data.
>3 x ULN	and	Any		

Renal Impairment

No dose adjustments are recommended for bortezomib or selinexor in patients with renal insufficiency. There is no data in end-stage renal disease or hemodialysis.

Patients with compromised renal function should be monitored carefully when treated with bortezomib, especially if creatinine clearance is less than 30 mL/min. Bortezomib should be given after dialysis.

Dosage in the Elderly

No overall differences in effectiveness were observed in patients ≥ 65 years compared to younger patients. Older patients had a higher incidence of serious adverse reactions and discontinuation due to adverse reactions.

In elderly patients, the dexamethasone dose should be reduced (i.e. to 20 mg once weekly).

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F - Adverse Effects

Refer to bortezomib, selinexor drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection, bleeding (may be severe) • Nausea, vomiting	• Fatigue • Anorexia, weight loss • Diarrhea • Peripheral neuropathy	• Cataract, blurred vision (may be severe) • Cough, dyspnea • Constipation • Insomnia • Dizziness • Abnormal electrolyte(s) (may be severe) • Dysgeusia • Headache • Hypertension • Edema	• Hypotension • Cardiotoxicity • Arrhythmia • QTc prolongation • Arterial/venous thromboembolism • Pericarditis • Tumour lysis syndrome • Disseminated intravascular coagulation • Hemolytic uremic syndrome • GI obstruction, perforation • Pancreatitis • Hepatotoxicity • Nephrotoxicity • Hypersensitivity • Pulmonary hypertension • Pneumonitis • Cognitive disturbance, confusion • PML • PRES • Seizure • Graft loss

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G - Interactions

Refer to bortezomib, selinexor drug monograph(s) for additional details.

- Avoid bortezomib co-administration with strong CYP3A4 inducers. Monitor for selinexor efficacy if co-administered with moderate or strong CYP3A4 inducers.
- Monitor closely for bortezomib toxicity if co-administered with moderate or strong CYP3A4 inhibitors.
- Avoid green tea and preparations containing green tea during bortezomib treatment.
- Avoid vitamin C supplementation during bortezomib treatment.
- Monitor blood glucose with drugs that cause hypoglycemia.
- Monitor for additive effects with drugs that cause neuropathy and hypotension.

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H - Drug Administration and Special Precautions

Refer to bortezomib, selinexor drug monograph(s) for additional details.

Administration: Bortezomib

- Bortezomib may be administered:
  - Intravenously (1 mg/mL concentration) as a 3 to 5 second bolus injection or
  - Subcutaneous (2.5 mg/mL concentration)
- Bortezomib should only be reconstituted with 0.9% sodium chloride injection.
- Bortezomib is FATAL IF GIVEN INTRATHECALLY.
- Bortezomib has a **narrow therapeutic range**. **If a different reconstituted concentration is used for each route of administration, exercise caution when reconstituting and calculating the dose volume.**
- If local injection site reactions occur following subcutaneous bortezomib, consider using a less concentrated solution subcutaneously (1 mg/mL), or administer as IV.
- For subcutaneous use, bortezomib solution is injected into the right or left sides of the thighs or abdomen. Rotate injection sites with subsequent injections. Give new injections at least 2.5 cm from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.
- Unopened vials may be stored between 15 and 30º C. Retain in original package and protect from light.

Administration: Selinexor

- Administer selinexor with or without food.
- Tablets should be swallowed whole with a glass of water. Do not break, chew, crush, or divide tablets.
- If a dose is missed, the patient should skip this dose and take the next dose as scheduled.
- If the patient vomits after a dose, the dose should not be repeated. Patients should take the next dose as scheduled.
- Store between 2 to 30°C.

Contraindications

- Patients who have a hypersensitivity to these drugs or any of their components including boron and mannitol
- Bortezomib is NOT for intrathecal use. Fatal if given intrathecally.

Warnings/Precautions

- Severe hyponatremia or neurological toxicities, including life-threatening events, have occurred with selinexor.
- Caution should be exercised when driving or using machinery, especially in patients at risk of hypotension, dehydration or with a history of syncope; hypotension, dizziness, blurred vision, and confusion have been reported.
- Use bortezomib with caution in patients with concurrent multiple myeloma and AL amyloidosis, or patients with risk factors for seizures.
- Use bortezomib with caution in patients with risk factors for or existing cardiac disease.
- Use with caution in patients with pre-existing peripheral or autonomic neuropathy; patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment.

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Probable

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline, before each cycle (more frequent during the first 3 months), and as clinically indicated.
- Electrolytes (including sodium*); Baseline, before each cycle (more frequent during the first 2 months), and as clinically indicated
- Weight, nutritional and hydration status; Baseline, before each cycle, and as clinically indicated
- Liver function tests; Baseline, before each cycle, and as clinically indicated
- Renal function tests; Baseline, before each cycle, and as clinically indicated
- Blood glucose levels; Baseline and as clinically indicated
- Chest x-ray; Baseline, then CXR and lung function assessment if ILD is suspected
- Clinical toxicity assessment of fatigue, hypotension, neurotoxicity, infection, bleeding, respiratory symptoms, tumour lysis syndrome, cardiovascular, skin, ocular, neurologic and GI side effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

*Sodium levels may appear lower with concurrent hyperglycemia (serum glucose > 8.3 mmol/L) and high serum paraprotein levels; use corrected Na levels.

Suggested Clinical Monitoring

- LVEF monitoring in patients with cardiac risk factors; Baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	0.5 hr
Pharmacy Workload (average time per visit)	16.369 minutes
Nursing Workload (average time per visit)	27.5 minutes

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K - References

Bahlis NJ, Sutherland H, White D, et al. Selinexor plus low-dose bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma.Blood.2018;132(24):2546-2554.

Bortezomib drug monograph. Ontario Health (Cancer Care Ontario).

CADTH reimbursement recommendation: selinexor (multiple myeloma). August 2022.

Selinexor drug monograph. Ontario Health (Cancer Care Ontario).

March 2024 Expanded into full regimen monograph

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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