Regimen Monograph

A - Regimen Name

BORTDEXADARA Regimen

Bortezomib-Dexamethasone-Daratumumab

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 the treatment of patients with multiple myeloma with good performance status who have received at least one prior therapy

Supplementary Public Funding

bortezomib
New Drug Funding Program (Bortezomib - Relapsed or Refractory Multiple Myeloma)

daratumumab
New Drug Funding Program (Daratumumab - In Combination with Bortezomib and Dexamethasone for Relapsed Multiple Myeloma)

dexamethasone
ODB - General Benefit (dexamethasone) (ODB Formulary)

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B - Drug Regimen

Note: Different daratumumab products are NOT INTERCHANGEABLE.

Cycles 1 to 3:

bortezomib	1.3 mg /m²	Subcut	Days 1, 4, 8 and 11
daratumumab*	16** mg /kg	IV	Days 1, 8 and 15
dexamethasone^	20 mg	PO	Days 1, 2, 4, 5, 8, 9, 11, 12

Cycles 4 to 8:

bortezomib	1.3 mg /m²	Subcut	Days 1, 4, 8 and 11
daratumumab*	16 mg /kg	IV	Day 1
dexamethasone^	20 mg	PO	Days 1, 2, 4, 5, 8, 9, 11, 12

See DARA(MNT) for Cycles 9 and beyond

Alternative Schedule (with bortezomib weekly):

Cycles 1 to 3:

bortezomib	1.3 mg /m²	Subcut	Days 1, 8, 15
daratumumab*	16** mg /kg	IV	Days 1, 8, 15
dexamethasone†, ^	40 mg	PO	Days 1, 8, 15

Cycles 4 to 8:

bortezomib	1.3 mg /m²	Subcut	Days 1, 8, 15

daratumumab*	16 mg /kg	IV	Day 1
dexamethasone†, ^	40 mg	PO	Days 1, 8, 15

See DARA(MNT) for Cycles 9 and beyond

*Daratumumab infusion should be administered at the appropriate initial infusion rate with incremental escalation. Subsequent infusion rate escalation or dilution reduction should only be considered if the previous infusion was well-tolerated. See the Administration section for details.

**Splitting the first dose over 2 days has been described (8 mg/kg days 1 and 2) and may be considered. The same pre-medications should be administered prior to both treatment days (Reece et al 2018). See Premedication and Supportive Measures section for details.

†Dexamethasone may be given as 20 mg pre-medication, on the days of daratumumab infusion, and 20 mg post-medication, on the days after the infusion.

^Consider reducing the dexamethasone dose in elderly patients.

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C - Cycle Frequency

CYCLES 1 TO 8: EVERY 21 DAYS

Refer to DARA(MNT) for CYCLES 9 AND BEYOND (Daratumumab monotherapy REPEAT EVERY 28 DAYS until disease progression or unacceptable toxicity)

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Supportive care:

- HBV screening should be performed in all patients prior to starting daratumumab.
- Daratumumab can interfere with cross-matching for blood transfusions; type and screen and RBC genotyping tests should be done before starting this drug.
- Consider antiviral prophylaxis for herpes zoster reactivation.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Pre-medications (prophylaxis for infusion reaction):

To be given at least 1 hour prior to daratumumab infusion:

- Dexamethasone 20 mg IV/PO*
- Oral antipyretic (e.g. acetaminophen 650-1000 mg)
- H1-receptor antagonist IV/PO (e.g. diphenhydramine 25-50 mg or equivalent)
- Famotidine 20 mg IV (or equivalent)
- Montelukast 10 mg PO**

*Administer IV prior to the first infusion; Oral administration may be considered prior to subsequent infusions. Dexamethasone on the day of infusion may be given as part of pre-/post-medications for daratumumab; 20 mg IV/PO on the day of daratumumab infusion and 20 mg PO on the day after infusion. For patients receiving reduced dose dexamethasone 20 mg weekly, the entire 20 mg dose has been given prior to the daratumumab infusion in some clinical trials.

**The addition of montelukast given prior to the first infusion numerically reduced the incidence of respiratory IRs in the study by Nooka et al.

Post-infusion medications (prevention of delayed reactions):

- Dexamethasone 20 mg PO on the day after daratumumab infusion*
- Consider bronchodilators (e.g. short and long acting) and inhaled corticosteroids if chronic obstructive pulmonary disorder&****

*Dexamethasone on the day of infusion may be given as part of pre-/post-medications for daratumumab; 20 mg IV/PO on the day of daratumumab infusion and 20 mg PO on the day after infusion. For patients receiving reduced dose dexamethasone 20 mg weekly, the entire 20 mg dose has been given prior to the daratumumab infusion in some clinical trials.

&Consider adding an H1-receptor antagonist if the patient is at higher risk of respiratory complications.

***These may be discontinued after the 4th infusion if no major IRs occurred.

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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

Daratumumab dose reductions are not recommended. Doses were held for toxicity as suggested below and missed doses were not made up. Discontinue daratumumab if a dose is delayed by more than 28 days.

For bortezomib, dose reductions were permitted at the following dose levels:

Dose level	Bortezomib Dose (mg/m^2)
0	1.3
-1	1
-2	0.7
-3	Discontinue

Table A - Suggested Dose Modifications:

Toxicity	Severity	Daratumumab dose	Bortezomib Dose
Neutropenia	Grade 3 without complications	No change	No change; consider adding G-CSF
	Febrile neutropenia or Grade 4	Hold until ≤ grade 2	Hold until recovery to baseline or ≤ grade 2. Restart at the current dose and consider G-CSF support. If recurs, restart at 1 dose level reduction.
Thrombocytopenia	Grade 3 with bleeding or Grade 4	Hold until ≤ grade 2	Hold until recovery to baseline or ≤ grade 2. Restart at 1 dose level reduction.
Non-hematologic toxicity*	Grade 3 or higher	Hold until ≤ grade 2	If bortezomib-related, hold until

			recovery to ≤ grade 2. Restart at 1 dose level reduction.
PRES/PML/pneumonitis/dose limiting bortezomib toxicity at 0.7 mg/m2 dose	Any grade	n/a	Discontinue
HBV reactivation	Any	Hold treatment (including steroids). Consult with a HBV expert and manage appropriately. Restart of treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.	

*except grade 3 nausea/vomiting/diarrhea that responds to antiemetics/antidiarrheals; grade 3 isolated GGT elevation; grade 3 fatigue present at baseline or that lasts for < 7 days after the last administration of daratumumab; neurotoxicity with bortezomib (see table B); infusion-related reaction with daratumumab (see table C)

Table B - Bortezomib Dosage with Neurotoxicity:

Severity of Neurotoxicity	Bortezomib Dose
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
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)	Hold bortezomib until toxicity resolves. When toxicity resolves reinitiate at a reduced dose of 0.7mg/m^2 and give once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis, and/or severe autonomic neuropathy)	Discontinue permanently

Table C - Management of Daratumumab Infusion-related Reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a rate of no more than 50% of the rate at which the reaction occurred. • If no reaction occurs, escalate the rate at no more than 50 mL/hour every hour.	• Re-challenge with pre-medications and with infusion rate modification (eg. Table D in Drug Administration and Special Precautions section).
3	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a rate of no more than 50% of the rate at which the reaction occurred. • If no reaction occurs, escalate the rate at no more than 50 mL/hour every hour.	• Re-challenge with pre-medications and with infusion rate modification (eg. Table D in Drug Administration and Special Precautions section). • If a grade 3 IR recurs for the 3rd time, discontinue permanently (do not re-challenge).
4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Hepatic Impairment

Hepatic Impairment	Daratumumab Dose
Mild (total bilirubin 1 to 1.5 times ULN or AST > ULN)	No dose adjustment necessary
Moderate (total bilirubin >1.5 to 3 times ULN and any AST)	No data
Severe impairment (total bilirubin >3 times ULN and any AST)	

Bortezomib is metabolized by liver enzymes and exposure is increased in patients with moderate to severe hepatic impairment. Patients with hepatic impairment should be treated with extreme caution and should be closely monitored for toxicities, and dose reduction should be considered.

Suggested dose modifications:

Bilirubin	AST	Bortezomib Starting Dose
≤ 1 times ULN	> ULN	No change
> 1 – 1.5 times ULN	Any	No change
> 1.5 – 3 times ULN	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.
> 3 times ULN	Any	

Renal Impairment

Dose adjustments for bortezomib and daratumumab are not necessary in patients with renal insufficiency.

Formal studies have not been conducted with daratumumab; the drug is not renally cleared.

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

Dosage in the Elderly

No dose adjustments necessary for bortezomib or daratumumab. No overall differences in effectiveness was observed for daratumumab, but the incidence of serious adverse reactions (e.g., pneumonia) was more frequent in older patients.

Consider reducing the dexamethasone dose in elderly patients.

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F - Adverse Effects

Refer to bortezomib, daratumumab, dexamethasone 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 ± bleeding, infection (includes atypical infection, viral reactivation; may be severe)	• Infusion-related reaction with daratumumab (includes CRS / anaphylaxis; may be severe) • Neuropathy (may be severe) • Diarrhea • Cough, dyspnea	• Edema • Fatigue • Constipation (may be severe) • Musculoskeletal pain • Insomnia • Nausea, vomiting • Hypotension (may be severe) • Anorexia • Headache • Dizziness • Abnormal electrolytes • Corticosteroid effects (GI irritation, mood changes, hyperglycemia, insomnia)	• Arrhythmia, QT prolongation • Cardiotoxicity • Pulmonary hypertension • Arterial/venous thromboembolism • DIC • Nephrotoxicity • Nephrotic syndrome • Hemolytic uremic syndrome • Hepatotoxicity • Pancreatitis • GI obstruction/ perforation • Hypersensitivity • ↓Immunoglobulins • Pneumonitis • Seizures • PRES / PML • Secondary malignancy • Tumour lysis syndrome • Optic neuritis • Seizure • Graft loss • Corticosteroid effects (osteoporosis, cataracts)

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G - Interactions

Refer to bortezomib, daratumumab, dexamethasone drug monograph(s) for additional details

- Daratumumab interferes with indirect antiglobulin (Coombs) test by binding to CD38 on RBCs. Daratumumab-mediated positive Coombs test may persist for up to 6 months after treatment completion. Blood should be typed and screened prior to initiating treatment. Notify blood transfusion centres of this in the event of a planned transfusion and educate patients.
- Daratumumab may interfere with the serum protein electrophoreses (SPE) and immunofixation (IFE) assays used to monitor M-protein. This can impact the monitoring of response and disease progression in some patients with IgG kappa myeloma protein.
- Use bortezomib with caution with strong CYP3A4 inhibitors; monitor for toxicity
- Avoid strong CYP3A4 inducers if possible; monitor for reduced bortezomib efficacy
- Avoid use of green tea and vitamin C during bortezomib treatment
- Exercise caution and monitor blood glucose when co-administered with hypoglycemic agents
- Exercise caution and monitor with drugs associated with neuropathy or hypotension

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H - Drug Administration and Special Precautions

Refer to bortezomib, daratumumab, dexamethasone 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 to protect from light.

Daratumumab

Daratumumab IV and subcutaneous formulations are **not interchangeable**. The dosing and administration of these products are different.

- Daratumumab infusion should be administered at the appropriate initial infusion rate with incremental escalation. Subsequent infusion rate escalation or dilution reduction should only be considered if the previous infusion was well-tolerated (Table D).

Table D: Standard infusion rates

	Dilution volume	Initial Infusion Rate (1st hr)	Increments of infusion rate	Max infusion rate	Approximate infusion time
Week 1 (single dose infusion)	1000 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	6.5 hr
Week 1 (split dose infusion; applicable to days 1 and 2)	500 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	4 hr
Week 2[a]	500 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	4 hr
Subsequent Infusions[b,c]	500 mL	100 mL/hr	50 mL/hr every hour	200 mL/hr	3.25 hr

[a] If single dose infusion is used for week 1, the 500 mL dilution volume for the 16 mg/kg dose should be used only if there were no IRRs in the previous week.

[b] Initial infusion rate should only be modified if treatment in Weeks 1 and 2 were well-tolerated (no ≥ grade 1 IRRs during ≥100 mL/hr).

[c] If the patient did not experience an IR in the first 2 infusions of daratumumab, consideration can be given to administer daratumumab as a rapid infusion starting with the 3rd dose (20% of the dose over 30 minutes at 200 mL/hour, then the remaining 80% of the dose over 60 minutes at 450 mL/hour).

- Missed doses should be administered as soon as possible and the dosing schedule adjusted accordingly. The treatment interval should be maintained.
- Daratumumab should be diluted in 0.9% Sodium Chloride; remove a volume from the IV bag that is equal to the required volume of daratumumab solution.
- Daratumumab solution is colourless to yellow.
- The diluted solution may develop very small, translucent to white proteinaceous particles. Do not use if opaque particles, discolouration, or other foreign particles.
- Administer by IV infusion using an infusion set with a flow regulator and an in-line, low protein-binding filter (0.22 or 0.2 µm).
- The infusion bag must be made of PVC, polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE).
- Polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE administration sets must be used.
- Do not infuse concomitantly in the same IV line with other agents.
- Store vials at 2^{o}C - 8^{o}C
- Do not shake or freeze, protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Dexamethasone:

- Oral tablets for self-administration
- Given with food, preferably in the morning
- Store tablets at room temperature

Contraindications

- Patients with hypersensitivity to bortezomib, boron, mannitol, daratumumab or any ingredients

in the formulations or components of the containers

- Bortezomib is NOT for intrathecal use. Fatal if given intrathecally

Warnings/Precautions

- Daratumumab can cause severe infusion-related reactions (IRRs), including anaphylaxis. It should only be administered by healthcare professionals with appropriate medical support to manage these reactions. Pre and post infusion medications should be administered (see Premedication and Supportive Measures section).
- Caution should be exercised when driving or using machinery, and in patients on medication(s) that may lead to hypotension, or patients with dehydration or history of syncope, due to the risk of hypotension and dizziness.
- 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 bortezomib 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 and Lactation:

- Daratumumab and bortezomib should not be used during pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.
- Breastfeeding is not recommended.
- Fertility Effects:
  - Daratumumab: Unknown
  - Bortezomib: 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.

Recommended Clinical Monitoring

- Blood; Type and screen prior to starting daratumumab. In the event of a planned transfusion, notify blood transfusion centres.
- CBC with differential; baseline, before each cycle and as clinically indicated
- Chest x-ray; baseline, then CXR and lung function assessment if ILD is suspected
- Liver and renal function tests, electrolytes ; baseline and as clinically indicated
- HBV serology; Baseline for all patients and as clinically indicated. For patients with evidence of HBV serology at baseline, monitor during treatment and for at least 6 months post treatment. Consult with an expert in HBV.
- Blood glucose levels, especially in patients using antidiabetic medications; baseline and as clinically indicated
- Immunoglobulin levels; baseline and as clinically indicated
- Clinical toxicity assessment for infusion-related reactions, infection, anemia, bleeding, fatigue, hypotension, neurotoxicity, respiratory problems, musculoskeletal pain, tumour lysis syndrome, skin changes, neurologic, GI and cardiovascular effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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	2.5 to 7.5 hours (depending on duration of daratumumab infusion); bortezomib only: 0.5 hour
Pharmacy Workload (average time per visit)	29.794 minutes
Nursing Workload (average time per visit)	46.17 minutes

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K - References

Bortezomib and daratumumab drug monographs, Cancer Care Ontario.

Gut N, Yucebay F, Dempsey J, et al. Efficacy of once-weekly bortezomib with daratumumab for patients with relapsed or refractory multiple myeloma. Blood 2018;132:1958.

Nooka AK, Gleason C, Sargeant MO, et al. Managing infusion reactions to new monoclonal antibodies in multiple myeloma: daratumumab and elotuzumab. J Oncol Pract 2018 Jul;14(7):414-22.

Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:754-66.

Palumbo A, Chanan-Khan A, Weisel K, et al. Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study. J Clin Oncol 2016;34, suppl;abstr LBA4.

PEBC Advice Documents or Guidelines

- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

September 2023 Updated the "Administrative Information" section with pharmacy and nursing workload

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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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