Regimen Monograph

A - Regimen Name

BORTDEXADARA(SC) Regimen

Bortezomib-Dexamethasone-Daratumumab (subcut)

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 have 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 (subcut)
New Drug Funding Program (Daratumumab - In Combination with Bortezomib and Dexamethasone for Relapsed Multiple Myeloma) (NDFP Website)

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

back to top

B - Drug Regimen

Note: Different daratumumab products are NOT INTERCHANGEABLE.

Cycles 1 to 3:

daratumumab (subcut)	1800 mg	Subcut	Days 1, 8 and 15
bortezomib	1.3 mg /m²	Subcut	Days 1, 4, 8 and 11
dexamethasone^	20 mg	PO	Days 1, 2, 4, 5, 8, 9, 11, 12

Cycles 4 to 8:

daratumumab (subcut)	1800 mg	Subcut	Day 1
bortezomib	1.3 mg /m²	Subcut	Days 1, 4, 8 and 11
dexamethasone^	20 mg	PO	Days 1, 2, 4, 5, 8, 9, 11, 12

See DARA(MNT-SC) for Cycles 9 and beyond

Alternative Schedule (with bortezomib weekly):

Cycles 1 to 3:

daratumumab (subcut)	1800 mg	Subcut	Days 1, 8, 15
bortezomib	1.3 mg /m²	Subcut	Days 1, 8, 15
dexamethasone† ,^	40 mg	PO	Days 1, 8, 15

Cycles 4 to 8:

daratumumab (subcut)	1800 mg	Subcut	Day 1
bortezomib	1.3 mg /m²	Subcut	Days 1, 8, 15
dexamethasone† ,^	40 mg	PO	Days 1, 8, 15

See DARA(MNT-SC) for Cycles 9 and beyond

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

^Consider reducing the dexamethasone dose in elderly patients.

back to top

C - Cycle Frequency

CYCLES 1 TO 8: EVERY 21 DAYS

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

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Low

- 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:

- 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 for Daratumumab (subcut) (prophylaxis for administration-related reactions (ARR)):

To be given at least 1 hour prior to each dose:

- Dexamethasone 20 mg IV/PO †
- Antipyretic PO (e.g., acetaminophen 650-1000 mg)
- H1-receptor antagonist IV/PO (e.g., diphenhydramine 25-50 mg or equivalent)
- Montelukast 10 mg PO‡

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

‡Montelukast 10 mg was optional on Cycle 1 Day 1 during clinical trials of daratumumab (subcut). The addition of montelukast given prior to the first daratumumab IV infusion numerically reduced the incidence of respiratory infusion reactions in the study by Nooka et al.

Post-Injection Medications for Daratumumab (subcut) (prevention of delayed ARRs):

- Dexamethasone 20 mg PO for 1 day post-injection[¶,§]
- Consider bronchodilators (e.g., short and long acting) and inhaled corticosteroids (for patients with a history of COPD)[# ||]

[¶]Dexamethasone on the day of injection 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 injection. For patients receiving reduced dose dexamethasone 20 mg weekly, the entire 20 mg dose has been given prior to the daratumumab injection in some clinical trials.

[§]May discontinue after the third injection if no major systemic ARRs occurred (excluding regimen-specific corticosteroids).

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

[#]May be discontinued after the 4th injection if no major ARRs occurred.

back to top

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/m^2 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 (subcut) Administration-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 administration rate. • Manage the symptoms. **Restart:** • Consider restart if appropriate	• Consider rechallenge if appropriate.
3	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Consider restart if appropriate	• Consider rechallenge if appropriate.
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.

back to top

F - Adverse Effects

Refer to daratumumab (subcut), bortezomib, 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)	• Neuropathy (may be severe) • Diarrhea • Cough, dyspnea	• Edema • Fatigue • Constipation (may be severe) • Musculoskeletal pain • Insomnia • Nausea, vomiting • Administration-related reactions (may be severe) • 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 • Injection site reactions • Hypersensitivity • ↓Immunoglobulins • Pneumonitis • Seizures • PRES / PML • Secondary malignancy • Tumour lysis syndrome • Optic neuritis • Seizure • Graft loss • Corticosteroid effects (osteoporosis, cataracts)

back to top

G - Interactions

Refer to daratumumab (subcut), bortezomib, 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

back to top

H - Drug Administration and Special Precautions

Refer to daratumumab (subcut), bortezomib, 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 (subcut)

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

- Daratumumab (subcut) does not require reconstitution or dilution.
- Compatible with polypropylene or polyethylene syringe material, polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets, and stainless steel transfer and injection needles.
- Administer by subcutaneous injection, over approximately 3-5 minutes.
- Inject into the abdominal wall only (approximately 7.5 cm to the right or left of the navel). Do not give in areas where the skin is red, bruised, tender, hard or where there are scars.
- If pain occurs during injection, pause or slow rate of injection. If pain is not improved, the remaining dose may be given at an alternate injection site (on the opposite side of the abdomen).
- If there are other subcutaneous medications, they should be given at separate sites.
- Do not shake vials.
- Store vials at 2-8°C. Bring vials to room temperature (15-30°C) before use. Keep out of direct sunlight.

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 administration-related reactions (ARRs), including anaphylaxis. It should only be administered by healthcare professionals with appropriate medical support to manage these reactions. Pre and post injection 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:

- 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.
- If exposure to daratumumab occurred in utero, live vaccines should not be administered to the infant until a hematology evaluation has been completed.
- 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:
    - Daratumumab: Unknown
    - Bortezomib: Probable

back to top

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

- 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
- 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 systemic administration-related reactions, injection site 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

back to top

J - Administrative Information

Approximate Patient Visit	1.5 hours
Pharmacy Workload (average time per visit)	22.444 minutes
Nursing Workload (average time per visit)	41.792 minutes

back to top

K - References

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

Daratumumab (subcut) drug monograph, Ontario Health (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.

Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol. 2020 May;7(5):e370-e380.

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

November 2024 Updated Pregnancy and Lactation section

back to top

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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back to top