# BC Cancer Protocol Summary for the Treatment of Previously Untreated Multiple Myeloma Ineligible for Stem Cell Transplant using Daratumumab, Bortezomib, Lenalidomide and Dexamethasone

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

**ELIGIBILITY:**
Patients must:
- Have previously untreated multiple myeloma,
- Be ineligible or have no plan for stem cell transplant due to patient or clinical preference

Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca) is required

Patients should:
- Have good performance status
- Have adequate hematologic, renal and hepatic function

Notes:
- For patients who started alternate treatment prior to 1 Jul 2026 and wishing to switch to MYTIDBLDF, provider should submit a Compassionate Access Program (CAP) request
- Patients are eligible for only one line of anti-CD38 monoclonal antibody therapy (e.g., daratumumab or isatuximab).

**EXCLUSIONS:**
Patient must not:
- Have prior systemic therapy (except corticosteroids) or stem cell transplant for multiple myeloma
- Have clinical signs of meningeal involvement
- Be pregnant or breastfeeding
- Have AL amyloidosis without meeting criteria for multiple myeloma
- Have smoldering myeloma or monoclonal gammopathy of undetermined significance

**CAUTIONS:**
- ANC less than or equal to 1.0 x $10^9$/L (consider giving filgrastim),
- Platelet count less than 30 x $10^9$/L,
- CrCl less than 30 mL/min, or
- AST or ALT greater than or equal to 2.5 x upper limit of normal (ULN), total bilirubin greater than or equal to 1.5 x ULN

**TESTS:**

- Baseline (required before first treatment): Red Blood Cell phenotype and Group and Screen pre-daratumumab (mark on requisition “patient to start daratumumab”)
- Baseline (required before first treatment): CBC & Diff, creatinine, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose. If female of child-bearing potential (FCBP): Confirm negative pregnancy test results via a quantitative beta-hCG blood test obtained 7 to 14 days and 24 hours prior to initial prescription.
- 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, TSH, beta-2 microglobulin
- Baseline, if clinically indicated: urea, sodium, potassium
- 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)
- Every 4 weeks: CBC & Diff, creatinine, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH; if female of childbearing potential: quantitative beta-hCG blood test
- Days 8, 15, 22 (optional if pre-cycle cytopenias, hypercalcemia, hepatic or renal dysfunction 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
- Every three months (required for lenalidomide, but results do not have to be available to proceed with treatment): TSH
- If female of childbearing potential: Every week for 4 weeks during Cycle 1: quantitative beta-hCG blood test. Provider responsible for checking results.
- If clinically indicated: urea, sodium, potassium, HBV viral load (see protocol SCHBV)

**PREMEDICATIONS:**

- Prior to daratumumab administration:
  - acetaminophen 650 mg PO prior to each daratumumab
  - loratadine 10 mg PO (preferred) or diphenhydrAMINE 50 mg PO/IV prior to each daratumumab
  - montelukast 10 mg PO prior to daratumumab for Cycle 1 Day 1 then consider discontinuing if no infusion or injection reactions
  - If no reaction after 4 consecutive doses of daratumumab, may discontinue acetaminophen, loratadine/diphenhydrAMINE and montelukast
  - dexamethasone 20 to 40 mg PO prior to daratumumab for Cycle 1 only (the therapeutic dose of dexamethasone is used as the premedication steroid to reduce the risk of reactions). After Cycle 1, steroids are not required as a premedication as the risk of administration reactions is significantly reduced after the third dose of daratumumab. The therapeutic dexamethasone dose (if ordered) should be administered prior to daratumumab.
    - predniSONE may be used instead of dexamethasone as the therapeutic steroid. A minimum of 100 mg of predniSONE is required for Cycle 1. After Cycle 1, a lower dose of prednisone may be used and administered prior to daratumumab.

**SUPPORTIVE MEDICATIONS:**

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV), unless contraindicated (valACYclovir 500 mg PO daily)
- Routine anti-emetic or anti-diarrheal premedication is not required. These symptoms should be managed symptomatically if they arise
- Oral proton-pump inhibitor or $H_2$ antagonist for the duration of treatment with dexamethasone may be considered
- ASA (enteric coated), warfarin, direct oral anticoagulant (DOAC) PO or low molecular weight heparin (LMWH) SC daily continuing for the duration of treatment with lenalidomide

**TREATMENT:**

**Cycles 1 to 8:**
Insert a peripheral IV and saline lock for Cycle 1 Day 1 only for subcutaneous daratumumab, for use in the event of a hypersensitivity reaction.

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| dexamethasone | 40 mg[β] once weekly<br>on Days 1, 8, 15 and 22 | PO<br>prior to daratumumab, and on the weeks when daratumumab is not given, taken in the morning |
| lenalidomide | 25 mg once daily for 21 days<br>(Days 1 to 21) | PO, in the evening may be preferred |
| daratumumab | Cycles 1 and 2:<br>1800 mg (fixed dose in 15 mL)<br>on Days 1, 8, 15 and 22<br><br>Cycles 3 and 4:<br>1800 mg (fixed dose in 15 mL)<br>on Days 1 and 15<br><br>Cycles 5 to 8:<br>1800 mg (fixed dose in 15 mL)<br>on Day 1 only | subcutaneously over 5 minutes in the abdomen<br>Observe[¥] for 1 hour after administration on Day 1 of Cycle 1. Observation not required for subsequent doses, except at physician discretion |
| bortezomib | 1.3 mg/m$^2$ (may start with 1.5 mg/m$^2$)<br>on Days 1, 8, 15, and 22 | subcutaneously<br>(abdomen or thigh)[*] |

[¥] Observe patient for 1 hour after injection on Cycle 1 Day 1 only. If dyspnea, chills, rash, fever, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort occurs, page physician. Observation after subsequent doses at physician discretion only.
[*] Back of the arm can also be considered as a third option, after abdomen or thigh

- Repeat every 28 days for 8 cycles

**Cycle 9 and onward:**

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| dexamethasone | 40 mg[β] once weekly<br>on Days 1, 8, 15 and 22 | PO<br>prior to daratumumab, and on the weeks when daratumumab is not given, taken in the morning |
| lenalidomide | 25 mg once daily for 21 days<br>(Days 1 to 21) | PO, in the evening may be preferred |
| daratumumab | 1800 mg (fixed dose in 15 mL)<br>on Day 1 | Subcutaneously over 5 minutes in the abdomen |

[β]Dexamethasone dose may vary dependent on tolerability and co-morbidities. For older patients i.e. 75 years of age or older, the starting dose of dexamethasone should be 20 mg PO weekly. See also: Other options for steroid dosing, below. In patients 75 years of age or older, consideration may also be given to discontinuing dexamethasone after 2 cycles if patient is responding well to treatment. The risk of reactions is significantly reduced after the third dose of daratumumab; therefore, premedication with steroids is not required after Cycle 1.

- Each cycle is 28 days.
- Treat until disease progression or unacceptable toxicity.

**Vital signs monitoring: subcutaneous daratumumab**

Vital signs immediately prior to the injection, at the end of the injection, and at the end of observation period for first injection only (Cycle 1 Day 1), and as needed.

**POST INFUSION MEDICATIONS:**

Patients with a higher risk of respiratory complications (e.g., patients with chronic obstructive pulmonary disease (COPD) who have a forced expiratory volume in 1 second of less than 80%; patients with asthma) should be treated with post-infusion medication consisting of an antihistamine (diphenhydramine) on the first and second days after all infusions, short acting adrenergic receptor agonist (salbutamol inhaler), and control medications for lung disease (e.g., inhaled corticosteroids +/- long-acting β2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators +/- inhaled corticosteroids for patients with COPD).

## 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:**<br>dexamethasone 20 mg PO once weekly (or dexamethasone 4 to 40 mg PO once weekly based on toxicity and patient tolerance) |
| **Option B:**<br>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:**<br>No dexamethasone/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 with high-dose steroids. High dose steroids may be added for non-response. In Cycle 1, hydrocortisone 100 mg IV should be considered prior to each daratumumab dose for prevention of IRR. |

## DOSE MODIFICATIONS:

## LENALIDOMIDE DOSE MODIFICATIONS:

- NB: Use one of the 25 mg, 20 mg, 15 mg, 10 mg, 5 mg or 2.5 mg capsules for dosing. Currently there is no evidence to support the use of other dosing regimens (i.e., there is no clinical reason or research available to support the use of a combination of lenalidomide capsules for dosing, however the use of such dosing does have significant budgetary implications).
- Dexamethasone (or predniSONE) should continue to be taken even if lenalidomide is held due to a dose limiting toxicity.

### Lenalidomide Dose Levels:

| Dose Level 0 | Dose Level -1 | Dose Level -2 | Dose Level -3 | Dose Level -4 | Dose Level -5 |
|---|---|---|---|---|---|
| 25 mg | 20 mg | 15 mg | 10 mg | 5 mg | 2.5 mg |

### Bortezomib dose levels:

| Dose Level 0 | Dose Level -1 | Dose Level -2 | Dose Level -3 | Dose Level -4 |
|---|---|---|---|---|
| 1.5 mg/m$^2$ | 1.3 mg/m$^2$ | 1 mg/m$^2$ | 0.7 mg/m$^2$ | 0.5 mg/m$^2$ |

**1. Hematological (based on pre-cycle lab work):**

<table>
<tr><th>ANC (x10$^9$/L)</th><th></th><th>Platelets (x10$^9$/L)</th><th>Lenalidomide Dose</th><th>Bortezomib Dose</th><th>Daratumumab Dose</th></tr>
<tr><td>Greater than or equal to 1.0</td><td>and</td><td>Greater than or equal to 50</td><td>100%</td><td>Maintain dose level</td><td rowspan="4">100%</td></tr>
<tr><td>0.5 to 0.99†</td><td>or</td><td>30 to 49</td><td>Notify provider. Proceed but at next lower dose level, above.</td><td>Notify provider. Proceed but consider dose reduction by one dose level for low platelets.</td></tr>
<tr><td>Less than 0.5†</td><td>or</td><td>Less than 30*</td><td rowspan="2">Hold lenalidomide until ANC greater than or equal to 1.0 and platelets greater than or equal to 30, then restart at next lower dose level, above.</td><td>May proceed but decrease by one dose level if felt to be treatment-related.</td></tr>
<tr><td>Reoccurrence of less than 0.5†</td><td>or</td><td>Reoccurrence of less than 30*</td><td>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</td></tr>
</table>

* follow hematology weekly and consider arrangements for transfusion support as required.

† Consider weekly filgrastim (G-CSF) if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer.

## 2. Renal Dysfunction:

| Estimated GFR (eGFR)* or Creatinine clearance (mL/min) | Lenalidomide Dose | Bortezomib Dose | Daratumumab Dose |
|---|---|---|---|
| Greater than or equal to 60 | 25 mg daily† | 100%<br>For patients on hemodialysis, give dose after dialysis. | 100%<br>For daratumumab, no dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis. |
| 30 to less than 60 | 10 mg daily†‡ | | |
| Less than 30, not requiring dialysis | 15 mg every other day for 21 days, then rest for 7 days (i.e. 28-day cycle) | | |
| Less than 30, dialysis dependent | 5 mg daily† (administer after dialysis on dialysis day) | | |

*as reported in patient's laboratory report

†dosing for 21 days (Days 1 to 21) of each 28-day cycle

‡dose can be escalated to 15 mg after 2 cycles if patient is not responding to treatment and is tolerating the drug; may consider escalating to 25 mg if patient continues to tolerate the drug.

## 3. Hepatic Impairment:

| Severity | Total bilirubin | ALT | Bortezomib Dose |
|---|---|---|---|
| Mild | Less than or equal to 1 x ULN | Greater than the upper limit of normal | 100% |
| | Greater than 1 to 1.5 x ULN | Any | 100% |
| Moderate | Greater than 1.5 to 3 x ULN | Any | ▪ Reduce dose to 0.7 mg/m$^2$ in the first cycle.<br>▪ Consider dose escalation to 1 mg/m$^2$ or further dose reduction to 0.5 mg/m$^2$ in subsequent cycles based on patient tolerability. |
| Severe | Greater than 3 x ULN | Any | |

### 4. Non-Hematological/Non-Renal: lenalidomide

| Toxicity | Management |
|---|---|
| Grade 3 or greater exfoliative rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis | Discontinue |
| Pneumonitis | Hold and investigate; discontinue if confirmed. Note this is a very rare side-effect and alternative causes must be ruled out. |
| Grade 3 to 4 (any other toxicity) | Delay* then decrease by one dose level when dosing resumed at next cycle<br>Do not dose below 2.5 mg |

*Stop treatment immediately and delay until toxicity resolved to Grade 0-2

### 4. Peripheral Neuropathy: bortezomib

| Severity of Peripheral Neuropathy Signs and Symptoms | 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 1.3 $mg/m^2$ |
| Grade 2 with pain or Grade 3 (interfering with activities of daily living) | Delay until recovery. When resolved, reduce dose to 1 $mg/m^2$ x 2 doses |
| Grade 4 (permanent sensory loss that interferes with function) | Discontinue treatment |

### 5. Infusion Reactions

There are no modifications required to subcutaneous daratumumab for any current or previous infusion/administration reaction(s).

See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Chemotherapeutic Agents – SCDRUGRX.

## 6. Diarrhea: Bortezomib

*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 to 6 stools per day over baseline; IV fluids indicated for less than 24 h; 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 h; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living | Life-threatening consequences (e.g., hemodynamic collapse) |

| **Treatment of Diarrhea During Cycle** | | |
|---|---|---|
| At first loose stool: | Start loperamide 2 mg PO every 2 hours while awake and every 4 hours while sleeping. Continue around the clock until 12 hours diarrhea-free | • If diarrhea-free greater than 12 hours, stop loperamide. If new episode, retreat with loperamide.<br>• If Grade 3 diarrhea or diarrhea accompanied by mucus or dehydration, hold doses of bortezomib (if applicable) and hydrate. |

**Diarrhea Management: Next Cycle Dosing**

- Delay next cycle until diarrhea has resolved (less than 2 watery bowel movements per day)

| **Severity of diarrhea with *last* cycle:** | **Bortezomib dose *this* cycle** |
|---|---|
| Less than or equal to Grade 2 | No change from previous cycle |
| Greater than or equal to Grade 3<br>or<br>Associated with mucus or dehydration | Reduce dose to next dose level<br>(if two dose reductions have already occurred, further treatment with bortezomib must be individualized and should only continue if a clearly useful clinical response in the myeloma has occurred) |

**PRECAUTIONS:**

1. **Neutropenia**: fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Infusion/administration reactions** occur in approximately 15% of patients after subcutaneous injection and can be serious including bronchospasm, hypoxia and hypertension. These usually occur with the first dose and rarely after subsequent infusions. Nearly all reactions occurred shortly after completing the subcutaneous injection. Other signs and symptoms include cough, wheezing, larynx and throat tightness/irritation, laryngeal edema, pulmonary edema, nasal congestion, and allergic rhinitis. Less commonly reported symptoms include hypotension, headache, urticarial rash, pruritus, nausea, vomiting, and chills. Premedication with antihistamines, antipyretics, and corticosteroids is required; stop infusion for any infusion reactions and manage as appropriate. Administer in a facility with immediate access to resuscitative measures (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen). Consider administration of oral corticosteroids on the second day after administration to reduce the risk of delayed infusion reactions. Consider short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders; monitor closely. See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Chemotherapeutic Agents – SCDRUGRX.
3. **Interference with cross-matching and red blood cell antibody screening** occurs due to drug binding to CD38 on red blood cells (RBC) resulting in a positive Indirect Antiglobulin Test (Coombs test). This interference may persist for up to 6 months post last daratumumab treatment. Inform blood bank that a patient has received daratumumab. Type and screen patients prior to starting daratumumab.
4. **Interference with determination of myeloma response** as daratumumab (a human IgG kappa monoclonal antibody) may be detected on serum protein electrophoresis and immunofixation assays which monitor for endogenous M-protein. Interference with these assays by daratumumab may affect the determination of complete response and disease progression in some patients with IgG kappa myeloma protein.
5. **Venous thrombosis/embolism: Aspirin 81mg** oral daily should be considered in all patients. For those with higher risk of thromboembolic disease full anti-coagulation should be considered.
6. **Teratogenicity**: If lenalidomide is taken during pregnancy, it may cause severe birth defects or death to the fetus. Lenalidomide should never be used by females who are pregnant or who could become pregnant while taking the drug. Even a single dose taken by a pregnant woman may cause birth defects.
7. **Hepatotoxicity:** Hepatic failure, including fatal cases, has been reported in multiple myeloma patients treated with lenalidomide in combination with dexamethasone during post-marketing. The mechanism of severe drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes and concomitant medications may be risk factors. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
8. **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**.**
9. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
10. **Skin Rashes**: Lenalidomide may cause skin rashes although in general it is not severe. Minor rashes can be treated with diphenhydrAMINE and/or steroid creams and lenalidomide can be continued. Moderate rashes may require holding lenalidomide until resolution of the rash. For more severe rashes (greater than or equal to Grade 3: severe, generalized

erythroderma or macular, papular or vesicular eruption; desquamation covering greater than or equal to 50% BSA) lenalidomide should be discontinued.

11. **Live vaccines**: Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
12. **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.
13. **Hypothyroidism:** the use of lenalidomide may result in hypothyroidism. Treatment with thyroid replacement should be considered even for subclinical hypothyroidism. Lenalidomide can be continued if hypothyroidism can be easily managed.
14. **Second Primary Malignancies (SPM)**: In clinical trials of newly diagnosed multiple myeloma patients, for those receiving lenalidomide with dexamethasone, the hematological SPM incidence rate (0.14 per 100 person-years) was not increased as compared to patients on thalidomide in combination with melphalan and prednisone (0.91 per 100 person-years). The risk of occurrence of SPM must be taken into account before initiating treatment with lenalidomide. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.
15. **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.

**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. Usmani SZ, Facon T, Hungria V et al. Daratumumab Plus Bortezomib, Lenalidomide and Dexamethasone for Transplant-Ineligible or Transplant-Deferred Newly Diagnosed Multiple Myeloma: the Randomized Phase 3 CEPHEUS Trial. Nat Med 5 Feb 2025; 31(4), 1195-1202.
2. Daratumumab (Darzalex SC) Reimbursement Recommendation. Canada's Drug Agency (CDA-AMC). Canadian Journal of Health Technologies. Mar 2026; 6(3): 1-15.

## Appendix: Infusion Related Reaction

| Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|
| Mild transient reaction; infusion interruption not indicated; intervention not indicated | Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, iv fluids); prophylactic medications indicated for less than or equal to 24 hours | Prolonged (e.g., not rapidly responsive to symptomatic medication and /or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae | Life-threatening consequences; urgent intervention indicated | **Death** |