BC Cancer Protocol Summary for the Treatment of Previously Untreated Multiple Myeloma and Not Eligible for Stem Cell Transplant using Daratumumab, Lenalidomide and Dexamethasone

Protocol Code	*MYDARLDF*
Tumour Group	*Myeloma*
Contact Physicians	*Dr. Jesse Shustik* *Dr. Christopher Venner* *Dr. Kevin Song*

ELIGIBILITY:

Patients must have:
- Newly diagnosed multiple myeloma as per the updated International Myeloma Working Group criteria,
- Ineligibility for stem cell transplant,
- Life expectancy greater than 3 months,
- Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca), and

Note:
- Patients who are currently on first-line therapy started prior to 1 Jun 2022 may switch to MYDARLDF if they have not experienced progression and meet other eligibility criteria
- Patients are eligible for only one line of daratumumab therapy

CAUTION:
- Neutrophil count less than or equal to 1.0 x 10^9/L (consider giving filgrastim),
- Platelet count less than 75 x 10^9/L,
- Hemoglobin level of 75 g/L or less,
- Creatinine clearance less than 30 mL/min,
- AST or ALT or alkaline phosphatase level 2.5 or more times greater than the ULN, or
- Bilirubin of 1.5 or greater than the 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, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin. 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 lenalidomide prescription.
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with further treatment): HBsAg, HBcoreAb, serum protein electrophoresis, serum free light chain level, immunoglobulin panel, TSH

- If cytopenias a concern, every two weeks (for lenalidomide) during the first 4 cycles then may reduce frequency to every four weeks: CBC and diff, platelets, creatinine, calcium
- 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

Cycle 1 and Cycle 2

- Day 1: CBC & diff, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin. If female of childbearing potential: quantitative beta-hCG blood test
- Day 1 (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and free light chain levels.
- Day 1: (optional, results do not have to be available to proceed with treatment): immunoglobulin panel (IgA, IgG, IgM), urine protein electrophoresis
- Day 8, 15 and 22: CBC & diff, platelets. If clinically indicated, sodium, potassium, creatinine, ALT, serum bilirubin

Cycle 3 to Cycle 6

- Day 1: CBC & diff, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin. If female of childbearing potential: quantitative beta-hCG blood test.
- Day 1 (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and free light chain levels.
- Day 1: (optional, results do not have to be available to proceed with treatment): immunoglobulin panel (IgA, IgG, IgM), urine protein electrophoresis
- Day 15: CBC & diff, platelets. If clinically indicated, sodium, potassium, creatinine, ALT, serum bilirubin

Cycle 7 and subsequent

- Day 1**:** CBC & diff, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin. If female of childbearing potential: quantitative beta-hCG blood test
- Day 1 (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and free light chain levels.
- Day 1: (optional, results do not have to be available to proceed with treatment): immunoglobulin panel (IgA, IgG, IgM), urine protein electrophoresis

PREMEDICATIONS:

Prior to daratumumab administration (subcutaneous or intravenous):

- acetaminophen 650 mg PO prior to each daratumumab. Repeat acetaminophen Q4H x 1 dose during the IV infusion on Day 1 of cycle 1 only, then Q4H PRN
- loratadine 10 mg PO or diphenhydrAMINE 50 mg PO/IV prior to each daratumumab, then:
    - If using loratadine: give diphenhydrAMINE 50 mg IV Q4H PRN allergic reaction.
    - If using diphenhydrAMINE: repeat diphenhydrAMINE 50 mg Q4H X 1 dose during the IV infusion on Day 1 of cycle 1 only, followed by diphenhydrAMINE 50 mg IV Q4H PRN allergic reaction.
- montelukast 10 mg PO prior to daratumumab for cycle 1, day 1, (and day 2 if on alternative regimen), then consider discontinuing if no infusion or injection reactions
- 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). If using IV daratumumab split dosing (i.e., the Alternative regimen), dexamethasone 20 mg should be given prior to daratumumab on days 1 and 2. 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.[13] 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.

    Note: A minimum of 20 mg of dexamethasone (or 100 mg of predniSONE) is not needed prior to each daratumumab treatment after cycle 1

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.
- If Varicella-zoster Virus (VZV) seropositive, start valACYClovir 500 mg PO daily and continue for entire duration of daratumumab and for 4 weeks after discontinuation
- 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:

1 cycle = 28 days. Treat until progression

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 once weekly on days 1, 8, 15 and 22 *OR* For patients greater than 75 years of age (or younger than 75 years of age at MD's discretion), use dexamethasone 20 mg or lower once weekly on days 1, 8, 15 and 22	PO prior to daratumumab, and on the weeks when daratumumab is not given, taken in the morning
lenalidomide	25 mg once daily for 21 days (d 1-21)	PO, in the evening may be preferred
daratumumab¶	Cycles 1 and 2: 1800 mg (fixed dose in 15 mL) on days 1, 8, 15 and 22 Cycles 3 to 6: 1800 mg (fixed dose in 15 mL) on days 1 and 15 Cycles 7 and subsequent: 1800 mg (fixed dose in 15 mL) on day 1	subcutaneous over 5 minutes in the abdomen Observe¥ for 1 hour after administration on Day 1 of Cycle 1. Observation not required for subsequent doses, except at physician discretion

*Therapeutic dose of dexamethasone is used as the premedication steroid to reduce the risk of administration reactions. PrednisONE may be substituted for dexamethasone as the therapeutic steroid per physician preference. A minimum of 20mg dexamethasone or 100 mg prednisONE is required for cycle 1 only to prevent administration reactions. The risk of infusion reactions is significantly reduced after the third dose of daratumumab; therefore, premedication with steroids is not required after cycle 1.[13]

¥ 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. For patients changing from daratumumab IV to subcutaneous route, observe patient for 30 minutes after the first subcutaneous dose.

¶ Daratumumab may be given subcutaneously or intravenously. Subcutaneous daratumumab is the preferred route of administration due to decreased incidence of reaction and greater convenience. Patients who start on subcutaneous daratumumab, but require switch due to intolerance, may be administered IV daratumumab as per Cycle 2 plus guidelines below.

Vitals 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.

IV DARATUMUMAB Option:

If the intravenous route is chosen, there are 2 options for administering the first daratumumab infusion and the decision to use one over the other is centre-based:

1) **Standard regimen** – first infusion of daratumumab 16 mg/kg administered on Cycle 1 day 1. This is preferred where possible.

2) **Alternative regimen** – first dose of daratumumab is split over 2 days i.e., 8 mg/kg administered on Cycle 1 day 1 and again on day 2. Cycle 1 day 1 + day 2 is considered to be the first infusion. This regimen has been created to accommodate shorter clinic hours.

Cycle 1 DARATUMUMAB IV

Drug	Standard Regimen (Dose)	Alternative Regimen (Dose)	BC Cancer Administration Guideline
daratumumab	16 mg/kg on day 1		IV in 1000 mL NS (use 0.2 micron in-line filter) Start at 50 mL/h; if no reactions† after 60 minutes, increase rate by 50 mL/h every 60 minutes until maximum 200 mL/h
		8 mg/kg on days 1 and 2	IV in 500 mL NS (use 0.2 micron in-line filter) Start at 50 mL/h; if no reactions† after 60 minutes, increase by 50 mL/h every 60 minutes until maximum 200 mL/h
	16 mg/kg on day 8		IV in 500 mL NS (use 0.2 micron in-line filter) If no reaction on Cycle 1 day 1, or Cycle 1 day 1 and 2, or reaction is Grade 2‡ or less: Start infusion at 200 mL/h. If no reaction† after 30 minutes, infuse the remainder at 450 mL/h (rapid infusion) **OR** If reaction on Cycle 1 day 1, or Cycle 1 day 1 and 2 infusion is Grade 3‡: Start at 50 mL/h; if no reactions† after 60 minutes, increase by 50 mL/h every 60 minutes until maximum 200 mL/h (slow infusion)
	16 mg/kg on days 15 and 22		IV in 500 mL NS If no reaction on Cycle 1 day 1, day 2 and day 8 or reaction is Grade 2‡ or less: Start infusion at 200 mL/h. If no reaction† after 30 minutes, infuse the remainder at 450 mL/h (rapid infusion) **OR** If reaction on Cycle 1 day 1, day 2 and day 8 is Grade 3‡: Start at 100 mL/h; if no reactions† after 60 minutes, increase by 50 mL/h every 60 minutes until maximum 200 mL/h (slow infusion)

† If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort occurs, stop daratumumab infusion and page physician. See Infusion Reaction section in protocol for when to resume infusion and rate.

‡ For CTCAE grading, see Appendix: Infusion Related Reaction

Cycle 2 plus DARATUMUMAB IV

Drug	Cycle	Dose	BC Cancer Administration Guideline
daratumumab	Cycle 2	16 mg/kg on days 1, 8, 15, 22	IV in 500 mL NS (use 0.2 micron in-line filter) If no reaction in the previous infusion or reaction is Grade 2‡ or less: Start infusion at 200 mL/h. If no reaction† after 30 minutes, infuse the remainder at 450 mL/h (rapid infusion) **OR** If reaction in the previous infusion is Grade 3‡: Start at 100 mL/h; if no reactions† after 60 minutes, increase by 50 mL/h every 60 minutes until maximum 200 mL/h (slow infusion)
	Cycle 3 to 6*	16 mg/kg on days 1 and 15	
	Cycle 7≠ and subsequent	16 mg/kg on day 1	

† If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort occurs, stop daratumumab infusion and page physician. See Infusion Reaction section in protocol for when to resume infusion and rate.

‡ For CTCAE grading, see Appendix: Infusion Related Reaction

*For cycles 3 to 6, may order a maximum of 2 cycles at a time (i.e. return to clinic in 8 weeks)

≠For cycle 7 and onwards, may order a maximum of 3 cycles at a time (i.e. return to clinic in 12 weeks)

For additional information on infusion rates, see Appendix: Daratumumab infusion rate titration table.

Vitals monitoring: IV daratumumab

For infusions on Cycle 1 day 1 (and day 2, if using Alternative regimen)

Vital signs immediately before the start of the infusion, then every 30 minutes x 4, then every 1 to 2 hours until the end of the infusion. Post infusion at 30 minutes after the end of the infusion. Patient may leave when infusion is complete and patient is stable for 30 minutes.

For subsequent infusions i.e. Cycle 1 day 8 and beyond:

Vital signs immediately before the start and at the end of the infusion, and as needed. Patient may leave when infusion is complete and patient is stable for 30 minutes. Vitals and observation post-infusion not required after 3 treatments if patient did not experience any infusion reactions.

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

Option A: Oral dexamethasone 20 mg once weekly on days 1, 8, 15 and 22
Option B: PredniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance.
Option C: No steroid. 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. Hydrocortisone 100 mg IV should be given as a pre-medication prior to daratumumab in these cases to mitigate infusion reactions for Cycle 1 (see premedications). Steroids may be added for sub-optimal response.

DOSE MODIFICATIONS:

I. LENALIDOMIDE DOSE MODIFICATIONS:

Fatigue may respond to dose reduction

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.

1. Hematological:

Agent	Dose Level 0	Dose Level -1	Dose Level -2	Dose level -3	Dose level -4	Dose level -5
lenalidomide	25 mg	20 mg	15 mg	10 mg	5 mg	2.5 mg

ANC (x10^9/L)	Platelets (x10^9/L)	Lenalidomide Dose
Day 1 of Cycle less than 1.0	Day 1 of Cycle less than 30	Hold until ANC greater than or equal to 1.0 and platelets greater than or equal to 30† then consider dose reduction by 1 dose level* **Daratumumab start should also be delayed when lenalidomide cycle is being delayed.**
Day 15 of Cycle‡ less than 1.0	Day 15 of Cycle‡ less than 30	Omit for remainder of cycle; restart on Day 1 of next cycle if ANC greater than or equal to 1.0 and platelets greater than or equal to 30; consider reducing by 1 dose level*

*if filgrastim (5 mcg/kg) is available, resume at the same dose if delay due to ANC. Filgrastim is not covered as a benefit at the BC Cancer.

† follow hematology weekly

‡ Day 15 bloodwork for Cycle 1-4 will be monitored by the physician and physician will be responsible to check and advise patient on dose adjustment, as per suggested guidelines above.

For females of child-bearing potential on weekly pregnancy test during cycle 1, physician will be responsible for checking result

2. Non-hematological:

Renal dysfunction

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Lenalidomide Dose
greater than or equal to 60	25 mg daily†
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 (d 1-21) 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. Non-hematological/Non-renal

Toxicity	1st occurrence	2nd occurrence	3rd occurrence	4th or subsequent occurrence
Grade 3 or greater exfoliative rash, SJS, TEN	Discontinue			
Pneumonitis	For suspected pneumonitis, hold and investigate; discontinue if confirmed			
Grade 3-4 (any other toxicity)	Delay* then consider decreasing by one dose level when dosing resumed at next cycle	Delay* then consider decreasing by one dose level when dosing resumed at next cycle	Delay* then consider decreasing by one dose level when dosing resumed at next cycle	Delay* then consider decreasing by one dose level when dosing resumed at next cycle Do not dose below 2.5 mg

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

II. DARATUMUMAB DOSE MODIFICATIONS:

1. 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.

Infusion reactions	Management
If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort, stop infusion and page physician	**Initial occurrence:** After recovery of symptoms, restart infusion at HALF the rate at which the infusion reactions occurred and continue with escalation of infusion rates on the appropriate schedule above. **Subsequent occurrence:** If the infusion must be stopped a second time, restart after recovery of symptoms, at HALF the rate at which the infusion reactions occurred and continue at that rate without further escalation

Infusion rate when resuming infusion after grade 1 or greater symptoms are resolved:

Infusion rate when reactions occur	Maximum infusion rate when resuming infusion*
50 mL/h	25 mL/h*
100 mL/h	50 mL/h*
150 mL/h	75 mL/h*
200 mL/h	100 mL/h*
450 mL/h	225 mL/h*

*Incremental increases remain at 50 mL/h for all resuming infusions

2. Hematological†, for low counts due to treatment, not disease

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	daratumumab
Greater than or equal to 1.0		Greater than or equal to 50	100 %
Less than 1.0	and/or	Less than 50	Delay until recovery

†Modify on day 1 only. MD may delay or consider omitting on other days.

Consider holding lenalidomide, if daratumumab is delayed for cytopenias.
Dexamethasone (or predniSONE) does NOT need to be held.

3. Renal Failure:

For daratumumab, no dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis.

III. STEROID DOSE MODIFICATIONS

Dexamethasone (or predniSONE) does NOT need to be held when lenalidomide or daratumumab are held.

PRECAUTIONS:

1. **Infusion/administration reactions** occur in approximately 35 to 48% of all patients during intravenous infusions and in approximately 8 to 13% 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 during intravenous infusion or shortly after completing the infusion or 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 IV infusion for any infusion reactions and manage as appropriate. Reduce the infusion rate for grade 1, 2, or 3 infusion reactions, see Common Terminology Criteria for Adverse Events (CTCAE) in appendix; permanently discontinue therapy for grade 4 infusion reactions. 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
2. **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.
3. **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.
4. **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.
5. **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.
6. **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.
7. **Constipation**: Patients should be warned that constipation may occur in patients taking lenalidomide.

8. **Fatigue**: Patients should be warned that lenalidomide may cause fatigue. Fatigue may respond to dose reduction.
9. **Hepatitis B Reactivation**: All myeloma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamivudine 100 mg PO daily for the entire duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
10. **VZV prophylaxis:** Antiviral prophylaxis is recommended prior to initiating daratumumab for patients who are VZV seropositive. Patients should take valACYclovir 500 mg PO daily while taking daratumumab and for 4 weeks after its discontinuation. Of note, VZV serology is often not reliable, even in patients previously exposed. Most clinicians choose to prescribe valACYclovir without testing for VZV serology.
11. **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.
12. **Live vaccines**: Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
13. **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.
14. **Hypothyroidism:** the use of lenalidomide may result in hypothyroidism. Thyroid function tests should be repeated every 3 months. Treatment with thyroid replacement should be considered even for subclinical hypothyroidism. Lenalidomide can be continued if hypothyroidism can be easily managed.

Call Dr. Jesse Shustik or Dr. Christopher Venner (Lymphoma), or Dr. Kevin Song (Leukemia/BMT), or tumour group delegate with any problems or questions regarding this treatment program. (Lymphoma at (604) 877-6000 or 1-800-663-3333; Leukemia/BMT at (604) 875-4863 or after hours (604) 875-4111)

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Appendix:

Daratumumab infusion rate titration table

STANDARD Regimen Cycle 1: Day 1

Daratumumab 16 mg/kg IV in 1000 mL NS Total Volume (Refer to pharmacy label)		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
50 mL/h	1 h	50 mL
100 mL/h	1 h	100 mL
150 mL/h	1 h	150 mL
200 mL/h	3 h 30 min	700 mL

ALTERNATIVE Regimen Cycle 1: Day 1 and Day 2

Daratumumab 8 mg/kg IV in 500 mL NS Total Volume (Refer to pharmacy label)		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
50 mL/h	1 h	50 mL
100 mL/h	1 h	100 mL
150 mL/h	1 h	150 mL
200 mL/h	1 h	200 mL

Infusion rate is the same for both regimens thereafter.

Both regimens have same infusion rate for Cycle 1 Days 8, 15 and 22, and Cycle 2 and beyond.

Rapid Infusion: Cycle 1 Day 8 and beyond

Daratumumab 16 mg/kg IV in 500 mL NS **Total Volume (Refer to pharmacy label)**		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
200 mL/h	30 min	100 mL
450 mL/h	55 min	400 mL

Slow Infusion: Cycle 1: Day 8

Daratumumab 16 mg/kg IV in 500 mL NS **Total Volume (Refer to pharmacy label)**		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
50 mL/h	1 h	50 mL
100 mL/h	1 h	100 mL
150 mL/h	1 h	150 mL
200 mL/h	1 h	200 mL

Slow Infusion: Cycle 1: Day 15 and Day 22

Slow Infusion: Cycle 2 and beyond

Daratumumab 16 mg/kg IV in 500 mL NS **Total Volume (Refer to pharmacy label)**		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
100 mL/h	1 h	100 mL
150 mL/h	1 h	150 mL
200 mL/h	1 h 15 min	250 mL

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**

CTCAE v5.0-Nov.27, 2017