BC Cancer Protocol Summary for the Treatment of Relapsed and Refractory Multiple Myeloma with Daratumumab in Combination with Bortezomib and Dexamethasone With or Without Cyclophosphamide

Protocol Code	*MYDARBD*
Tumour Group	*Myeloma*
Contact Physicians	*Dr. Christopher Venner* *Dr. Jesse Shustik*

ELIGIBILITY:

Patients must have:
- Relapsed and refractory multiple myeloma,
- Received at least one prior line of therapy,
- Sensitivity to bortezomib, which includes patients who relapse after maintenance bortezomib (MYBORMTN), or have not previously been exposed

Note: Patients are eligible for only one line of anti-CD38 monoclonal antibody therapy (e.g., daratumumab or isatuximab). Re-use of anti CD-38 monoclonal antibody therapy can only be considered if not refractory to use in a prior line.

EXCLUSIONS:

Patients must not have:
- Disease refractory to bortezomib (progression on bortezomib-containing regimen other than MYBORMTN), or unacceptable side effects from bortezomib,
- Disease refractory to another proteasome inhibitor
- Prior progression on isatuximab-containing regimen

CAUTIONS:

- Neutrophils of 1.0 x 10^9/L or less (consider giving filgrastim),
- Platelet count of 30 x 10^9/L or less,
- AST or ALT level of 2.5 times greater than the ULN, or total 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, creatinine, sodium, potassium, urea, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
- 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, HBcoreAb, beta-2 microglobulin

- 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), beta-2 microglobulin
- Every 4 weeks: CBC & Diff, platelets, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
- Days 8, 15, 22 (optional if pre-cycle cytopenias, hypercalcemia, hepatic or renal dysfunction, or steroid-induced diabetes 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, platelets, creatinine, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, random glucose

PREMEDICATIONS:

Prior to daratumumab administration (subcutaneous or intravenous):

- acetaminophen 650 mg PO prior to each daratumumab, then Q4H PRN during infusion if infusion exceeds 4 hours
- loratadine 10 mg PO (preferred) 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 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.[15] 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 hepatitis B prophylaxis as per current guidelines
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating bortezomib and daratumumab. Patients should take valACYclovir 500 mg PO daily
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone may be considered

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	Cycle 1 to 8: 40 mg* once weekly on Days 1, 8, 15 and 22 Cycle 9 onwards: Optional at physician's discretion	PO prior to daratumumab, and on the weeks when daratumumab is not given, taken in the morning
cyclophosphamide (if using)	Cycle 1 to 8: 500 mg once weekly on Days 1, 8, 15, and 22 OR 50 mg once every 2 days Cycle 9 onwards: Optional at physician's discretion	PO, in the morning may be preferred
bortezomib≠	Cycle 1 to 8: 1.3 mg/m^2 (may start with 1.5 mg/m^2) once weekly on Days 1, 8, 15 and 22	subcutaneous (abdomen or thigh)
daratumumab¶	Cycles 1 and 2: 1800 mg (fixed dose in 15 mL) on Days 1, 8, 15 and 22 Cycles 3 and 4: 1800 mg (fixed dose in 15 mL) on Days 1 and 15 Cycles 5 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

*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. The risk of infusion reactions is significantly reduced after the third dose of daratumumab; therefore, premedication with steroids is not required after cycle 1.[15]

≠On days when both subcutaneous daratumumab and bortezomib are administered, give bortezomib before subcutaneous daratumumab.

¥ 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 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 (use 0.2 micron in-line filter) 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 450mL/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 4	16 mg/kg on Days 1 and 15	
	Cycle 5 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 cycle 9 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, 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

- 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: dexamethasone 20 mg PO once weekly (or dexamethasone 4 to 40 mg PO once weekly based on toxicity and patient tolerance)
Option B: 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: 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:

- **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):

ANC (x10^9/L) On Day 1		**Platelets (x10^9/L)** On Day 1	**Bortezomib Dose**	**Daratumumab Dose**	**Cyclophosphamide Dose (if using)**
Greater than or equal to 0.5	and	Greater than or equal to 50	Maintain dose level	100%	100%
Greater than or equal to 0.5	and	30 to 49	Notify provider. Proceed but consider dose reduction by one dose level for low platelets.	100%	Delay until recovery
Less than 0.5†	or	Less than 30*	May proceed but consider decrease by one dose level if felt to be treatment related.		
Reoccurrence of less than 0.5†	or	Reoccurrence of less than 30*	For recurrence 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		

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

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

2. Hepatic Impairment:

	Total bilirubin	ALT or AST	Bortezomib Dose	Daratumumab Dose	Cyclophosphamide Dose (if using)
Mild	less than or equal to 1 x ULN	greater than ULN	100%	100 %	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. ▪ 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			

3. Renal Dysfunction:

Bortezomib and daratumumab:

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Bortezomib Dose	Daratumumab Dose
Greater than or equal to 60	100% For patients on hemodialysis, give dose after dialysis.	100% For patients on hemodialysis, give dose after dialysis.
30 to 59		
Less than 30, not requiring dialysis		

Cyclophosphamide:

- Dose reduction is necessary per table, below. Physician may consider giving full dose of cyclophosphamide irrespective of renal function if deemed to be of benefit.
- For patients on hemodialysis, give dose after dialysis.

Creatinine clearance (mL/min)	Cyclophosphamide Dose
Greater than or equal to 10	100 %
Less than 10	75 %

Calculated creatinine clearance = $\frac{N \times (140 - Age) \times weight\ (kg)}{Serum\ Creatinine\ (micromols/L)}$

N = 1.04 (Females) and 1.23 (Males)

4. Peripheral Neuropathy: bortezomib

Severity of Peripheral Neuropathy Signs and Symptoms	Bortezomib 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 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living	Delay until recovery. When resolved, reduce dose to 0.7 mg/m^2 weekly
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

5. Diarrhea management with 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 – 6 stools per day over baseline; IV fluids indicated for less than 24hrs; 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 hrs; 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 q 2 h while awake and q4h while sleeping. Continue around the clock until 12 h diarrhea free	• If diarrhea free greater than 12 h, stop loperamide. If new episode, retreat with loperamide. • 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 / 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 or associated with mucus or dehydration	Reduce dose to 80% of that used in the last course or consider once a week dosing. (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)

6. Infusion/administration 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

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. **Hepatitis B Reactivation**: All myeloma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with hepatitis B prophylaxis according to current guidelines. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every three 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.
5. **Live vaccines**: Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
6. **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. .
7. **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.
8. **Diarrhea management with bortezomib:** see diarrhea management in bortezomib dose modification section.
9. **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.

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. Darzalex (daratumumab) [prescribing information], Horsham, PA: Janssen Biotech, Inc.; June 2017
2. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Eng J Med. 2015;373(13):1207-19.
3. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial. Lancet 2016;387(10027):1551-60.
4. Lokhorst HM, Plesner T, Gimsing P, et al. Phase I/II dose-escalation study of daratumumab in patients with relapsed or refractory multiple myeloma. ASCO 2013 abstract 8512.
5. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28:1122-1128
6. Venner CP, Connors JM, Sutherland HJ, et al. Novel agents improve survival of transplant patients with multiple myeloma including those with high-risk disease by early relapse (<12 months). Leuk Lymphoma, 2011:52:34-41
7. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016;375:1319-31
8. Bahlis NJ, Moreau P, Nahi H, et al. Daratumumab, Lenalidomide, Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in relapsed or Refractory Multiple Myeloma (RRMM): Efficacy and Safety Update (POLLUX). ASCO 2017 – Abstract 8025 / EHA Encore 2017 – Abstract P334.
9. Yimer HA, Melear J, Faber E, Do MS et al. Lyra: A Phase 2 Study of Daratumumab (Dara), Plus Cyclophosphamide, Bortezomib and Dexamethasone in Newly Diagnosed and Relapsed Patients (Pts) with Multiple Myeloma. ASCO 2018 – Abstract
10. Barr et al. Ninety-Minute Daratumumab Infusion is Safe in Multiple Myeloma. Leukemia 2018: 32(11): 2495-2518
11. Stakiw et al. initial results of MCRN 009: Phase 2 Study of an Accelerated Infusion Rate of Daratumumab in Patients with Relapsed/Refractory Multiple Myeloma (MM). 17th International Myeloma Workshop, September 12-15, 2019 – Abstract SP-102
12. Gozzetti et al. Long Term Safety and Efficacy of Daratumumab Rapid Intravenous Infusion (90minutes) After the Third Dose in Multiple Myeloma Patients. 17th International Myeloma Workshop, September 12-15, 2019—Abstract FP-160
13. Antonioli et al. Safety of rapid daratumumab infusion in relapsed and refractory multiple myeloma. 17th International Myeloma Workshop, September 12-15, 2019 – Abstract FP-149
14. Dimopoulos M, Sonneveld P, Leung N et al. International Myeloma Working Group Recommendations for the diagnosis and Management of Myeloma-Related Renal Impairment. J Clin Oncol 2016; 34 (13): 1544-57
15. Nahi H, Usmani SZ, Mateos MV et al. Corticosteroid tapering in patients (Pts) with relapsed or refractory multiple myeloma (RRMM) receiving subcutaneous daratumumab (DARA SC): Part 3 of the open-label, multicenter, phase Ib PAVO Study. ASCO Virtual Poster Presentation 2020, Abstract 8537.
16. Mateos M et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicenter, open-label, non-inferiority, randomized, phase 3 trial. Lancet Haematol 2020: 7(5):e370-80.
17. Chari A et al. Subcutaneous daratumumab plus standard treatment regimens in patients with multiple myeloma across lines of therapy (PLEIADES): an open-label Phase II study. British Journal of Haematology. July 2020
https://doi.org/10.1111/bjh.16980
18. Janssen Inc. DARZALEX® SC product monograph. Toronto, Ontario; 29 July 2020.
19. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia 2009; 23:1337-41.

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**

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