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

Protocol Code	*MYDARLD*
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 (which can include autologous stem cell transplant),
- Sensitivity to lenalidomide (which includes patients who relapse after maintenance lenalidomide, MYLENMTN) or have not previously been exposed, and
- Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca), and

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:

- Be refractory to lenalidomide (progression on lenalidomide-containing regimen other than MYLENMTN),
- Have prior progression on isatuximab-containing regimen,
- Be pregnant or lactating, or
- Have a known hypersensitivity to lenalidomide

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,
- AST or ALT greater than or equal to 2.5 x ULN, total bilirubin greater than or equal to 1.5 x ULN, or
- Known hypersensitivity to pomalidomide or thalidomide

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. 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, HBcoreAb, TSH, 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; if female of childbearing potential: quantitative beta-hCG blood test
- 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
- 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.

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 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 hepatitis B prophylaxis as per current guidelines
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating lenalidomide 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
- ASA (enteric coated), warfarin, direct oral anticoagulant (DOAC) or low molecular weight heparin (LMWH) subcutaneously daily continuing for the duration of treatment with lenalidomide

TREATMENT:

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	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 (Days 1 to 21)	PO, in the evening may be preferred
cyclophosphamide (if using)	Cycle 1 to 8: 500 mg once weekly onDays 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
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

* 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.[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.

1 cycle = 28 days. Treat until progression

- If a dose of lenalidomide is missed, take the next dose at the same usual time.
- If lenalidomide is resumed mid-cycle after being held for toxicity:
    - Stop on Day 21 as scheduled
    - Maintain at least 7 days rest before resuming next cycle

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

- 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:

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:

Drug	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

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

ANC (x 10^9/L) on Day 1		Platelets (x 10^9/L) on Day 1	Lenalidomide Dose	Daratumumab Dose	Cyclophosphamide Dose (if using)
Greater than or equal to 1.0	and	Greater than or equal to 50	100%	100%	100%
0.5 to 0.99†	or	30 to 49	Notify provider. Proceed but at next lower dose level, above.	100%	Delay until recovery
less than 0.5 or febrile neutropenia (ANC less than 1.0 with oral temperature greater than or equal to 38.0° Celsius)	or	less than 30*	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.		

* 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. Non-hematological: Renal dysfunction

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Lenalidomide Dose	Daratumumab Dose
greater than or equal to 60	25 mg daily†	100% 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.

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)

3. Non-hematological/Non-renal: lenalidomide

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

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 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.
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.

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.

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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**

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