Regimen Monograph

A - Regimen Name

DARA Regimen

Daratumumab

Disease Site

Hematologic
Multiple Myeloma

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and IMiD.

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B - Drug Regimen

Note: Different daratumumab products are NOT INTERCHANGEABLE.

Cycles 1 to 2:

daratumumab[1]	16* mg /kg	IV	Days 1, 8, 15, 22

(This drug is not currently publicly funded for this regimen and intent)

Q28 DAYS

Cycles 3 to 6:

daratumumab	16 mg /kg	IV	Days 1 and 15

Q28 DAYS

Cycle 7 and beyond:

daratumumab	16 mg /kg	IV	Day 1

Q28 DAYS

1 Daratumumab infusion should be administered at the appropriate initial infusion rate with incremental escalation. Subsequent infusion rate escalation or dilution reduction should only be considered if the previous infusion was well-tolerated. See the Administration section for details.

*Splitting the first dose over 2 days has been described (8 mg/kg days 1 and 2) and may be considered. The same premedications should be administered prior to both treatment days (Reece et al 2018). See Premedication and Supportive Measures section for details.

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

- Also refer to CCO Antiemetic Recommendations.
- HBV screening should be performed in all patients prior to starting daratumumab.
- Consider antiviral prophylaxis for herpes zoster reactivation.
- Daratumumab can interfere with cross-matching for blood transfusions; type and screen and RBC genotyping tests should be done before starting this drug.

Pre-medications (prophylaxis for infusion reaction):

To be given at least 1 hour prior to infusion:

- Corticosteroid IV (e.g. methylprednisolone 100 mg or equivalent)*
- Oral antipyretic (e.g. acetaminophen 650-1000 mg)
- H1-receptor antagonist IV/PO (e.g. diphenhydramine 25-50 mg or equivalent)
- Famotidine 20 mg IV (or equivalent)
- Montelukast 10 mg PO**

*This dose may be reduced following the second infusion (i.e. IV methylprednisolone 60 mg or equivalent).

**The addition of montelukast given prior to the first infusion numerically reduced the incidence of respiratory IRs in the study by Nooka et al.

Post-infusion medications:

- Oral corticosteroid (e.g. methylprednisolone 20 mg or equivalent) for 2 days post-infusion
- Consider bronchodilators (e.g. short and long acting) and inhaled corticosteroids if chronic obstructive pulmonary disorder ***

***These may be discontinued after the 4th infusion if no major IRs occurred.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

No dose reductions of daratumumab are recommended. A dose delay may be required in case of myelosuppression. Consider supportive care with transfusions or growth factors, as needed.

Hepatitis B virus (HBV) reactivation: Hold daratumumab, concomitant steroids and chemotherapy. Consult with a HBV expert and manage appropriately. Restart of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Table 1: Management of Infusion Reactions

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a rate of no more than 50% of the rate at which the reaction occurred. • If no reaction occurs, escalate the rate at no more than 50 mL/hour every hour.	• Re-challenge with pre-medications and with infusion rate modification (e.g. Table 2 in Drug Administration and Special Precautions section).
3	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a rate of no more than 50% of the rate at which the reaction occurred.	• Re-challenge with pre-medications and with infusion rate modification (e.g. Table 2 in Drug Administration and Special Precautions section). • If a grade 3 IR recurs for the 3rd time, discontinue permanently (do not re-challenge).

	• If no reaction occurs, escalate the rate at no more than 50 mL/hour every hour.	
4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Hepatic Impairment

Hepatic Impairment	Daratumumab Dose
Mild (total bilirubin 1 to 1.5 times ULN or AST > ULN)	No dose adjustment necessary
Moderate (total bilirubin >1.5 to 3 times ULN and any AST)	No data
Severe impairment (total bilirubin > 3 times ULN and any AST)	

Renal Impairment

No dose adjustment is necessary. Formal studies have not been conducted; daratumumab is not renally cleared.

Dosage in the Elderly

No dose adjustments necessary. No overall differences in effectiveness was observed, but the incidence of serious adverse reactions (e.g., pneumonia) was more frequent in older compared to younger patients.

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F - Adverse Effects

Refer to daratumumab drug monograph(s) for additional details of adverse effects.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Infusion related reaction (includes CRS / anaphylaxis, may be severe)	• Myelosuppression ± infection, bleeding (may be severe, including opportunistic infection or viral reactivation) • Fatigue • Cough, dyspnea • Musculoskeletal pain • Diarrhea • Nausea, vomiting	• Cardiotoxicity • Atrial fibrillation • Hepatotoxicity • Pancreatitis • ↓ Immunoglobulins • Renal failure

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G - Interactions

Refer to daratumumab drug monograph(s) for additional details.

- Daratumumab interferes with the indirect antiglobulin (Coombs) test by binding to CD38 on RBCs. Daratumumab-mediated positive Coombs test may persist for up to 6 months after treatment completion. Patient's blood should be typed and screened prior to initiating treatment. Notify blood transfusion centres of this in the event of a planned transfusion and educate patients.

- Daratumumab may interfere with the serum protein electrophoreses (SPE) and immunofixation (IFE) assays used to monitor M-protein. This can impact the monitoring of response and disease progression in some patients with IgG kappa myeloma protein.

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H - Drug Administration and Special Precautions

Refer to daratumumab drug monograph(s) for additional details.

Administration

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

- Daratumumab infusion should be administered at the appropriate initial infusion rate with incremental escalation. Subsequent infusion rate escalation or dilution reduction should only be considered if the previous infusion was well-tolerated (Table 2).

Table 2: Standard infusion rates

	Dilution volume	Initial Infusion Rate (1st hr)	Increments of infusion rate	Max infusion rate	Approximate infusion time
Week 1 (single dose infusion)	1000 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	6.5 hr
Week 1 (split dose infusion; applicable to days 1 and 2)	500 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	4 hr
Week 2[a]	500 mL	50 mL/hr	50 mL/hr every hour	200 mL/hr	4 hr
Subsequent Infusions[b, c]	500 mL	100 mL/hr	50 mL/hr every hour	200 mL/hr	3.25 hr

[a] If single dose infusion is used for week 1, the 500 mL dilution volume for the 16 mg/kg dose should be used only if there were no IRRs in the previous week.

[b] Initial infusion rate should only be modified if treatment in Weeks 1 and 2 were well-tolerated (no ≥ grade 1 IRRs during ≥100 mL/hr).

[c] If the patient did not experience an IR in the first 2 infusions of daratumumab, consideration can be given to administer daratumumab as a rapid infusion starting with the 3rd dose (20% of the dose over 30 minutes at 200 mL/hour, then the remaining 80% of the dose over 60 minutes at 450 mL/hour).

- Missed doses should be administered as soon as possible and the dosing schedule adjusted accordingly. The treatment interval should be maintained.

- Daratumumab should be diluted in 0.9% Sodium Chloride; remove a volume from the IV bag that is equal to the required volume of daratumumab solution.
- Daratumumab solution is colourless to yellow.
- The diluted solution may develop very small, translucent to white proteinaceous particles. Do not use if opaque particles, discolouration, or other foreign particles.
- Administer by IV infusion using an infusion set with a flow regulator and an in-line, low protein-binding filter (0.22 or 0.2 µm).
- The infusion bag must be made of PVC, polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE).
- Polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE administration sets must be used.
- Do not infuse concomitantly in the same IV line with other agents.
- Store vials at $2^{o}C$ - $8^{o}C$
- Do not shake or freeze, protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Patients with a history of severe hypersensitivity to daratumumab or who have hypersensitivity to any ingredient in the formulation or component of the container.

Other Warnings/Precautions

- Daratumumab can cause severe infusion-related reactions (IRRs), including anaphylaxis. It should only be administered by healthcare professionals with appropriate medical support to manage these reactions. Pre and post infusion medications should be administered (see Premedication and Supportive Measures section).

Pregnancy/Lactation:

- Daratumumab should not be used in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.
- Breastfeeding is not recommended.
- Fertility: Unknown

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; Baseline and before each dose
- Blood; Type and screen prior to starting daratumumab. In the event of a planned transfusion, notify blood transfusion centres.
- Electrolytes, renal function tests; Baseline and as clinically indicated
- Liver function tests; Baseline and as clinically indicated
- Immunoglobulin levels; Baseline and as clinically indicated
- HBV serology; Baseline for all patients and as clinically indicated. For patients with evidence of HBV serology at baseline, monitor during treatment and for at least 6 months post treatment. Consult with an expert in HBV
- Clinical toxicity assessment for infusion-related reactions, hypersensitivity, infection, anemia, bleeding, GI and cardiac effects; Baseline and at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	2.5 to 7.5 hours (depending on duration of daratumumab infusion)
Pharmacy Workload (average time per visit)	37.85 minutes
Nursing Workload (average time per visit)	74.833 minutes

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K - References

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

Lonial A, Weiss BW, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial. Lancet. 2016 Jan; 387: 1551-60.

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

Nooka AK, Gleason C, Sargeant MO, et al. Managing infusion reactions to new monoclonal antibodies in multiple myeloma: daratumumab and elotuzumab. J Oncol Pract 2018 Jul;14(7):414-22.

PEBC Advice Documents or Guidelines

- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

September 2022 Updated dose modifications, adverse effects, interactions, administration, pregnancy, and monitoring sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

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Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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