Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

DARADEXALENA(SC) Regimen

Daratumumab (subcut)-Dexamethasone-Lenalidomide

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:

- newly diagnosed multiple myeloma, in patients who are not eligible for autologous stem cell transplant and have good performance status
- patients with relapsed or refractory multiple myeloma who have received one or more prior lines of therapy

Supplementary Public Funding

daratumumab (subcut)
New Drug Funding Program (Daratumumab in Combination with Lenalidomide and Dexamethasone for Newly Diagnosed Transplant Ineligible Multiple Myeloma) (NDFP Website)

daratumumab (subcut)

New Drug Funding Program (Daratumumab - In Combination with Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma)

dexamethasone
ODB - General Benefit (dexamethasone) (ODB Formulary)

lenalidomide
ODB Limited Use (lenalidomide - For the treatment of patients with multiple myeloma, who are deemed to be lenalidomide sensitive, and/or have not experienced progression while on a lenalidomide-based regimen in the treatment or maintenance setting, according to clinical criteria) (ODB Formulary)

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B - Drug Regimen

Note: Different daratumumab products are NOT INTERCHANGEABLE.

Cycles 1 to 2 (Q28 days):

daratumumab (subcut)	1800 mg	Subcut	Days 1, 8, 15, 22
dexamethasone†	40** mg	PO	Days 1, 8, 15, 22
lenalidomide[1]	25 mg	PO	Days 1 to 21

Cycles 3 to 6 (Q28 days):

daratumumab (subcut)	1800 mg	Subcut	Days 1 and 15
dexamethasone†	40** mg	PO	Days 1, 8, 15, 22
lenalidomide[1]	25 mg	PO	Days 1 to 21

Cycle 7 and beyond (Q28 days):

daratumumab (subcut)†	1800 mg	Subcut	Day 1
dexamethasone†	40** mg	PO	Days 1, 8, 15, 22

lenalidomide[1]	25 mg	PO	Days 1 to 21

†Dexamethasone may be given as 20 mg pre-medication, on the days of daratumumab injection, and 20 mg post-medication, on the days after the injection.

**The dexamethasone dose should be reduced in elderly patients.

[1]Lenalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

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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 treatment.
- Daratumumab can interfere with cross-matching for blood transfusions; type and screen and RBC genotyping tests should be done before starting this drug.
- For lenalidomide, patients must be registered and meet all conditions of lenalidomide's controlled distribution program, including contraception.
- Women of child bearing potential must have two negative pregnancy tests before initiating treatment. Assess risk of second primary malignancies prior to starting treatment.
- Optimal control of thyroid function is recommended prior to starting lenalidomide treatment.
- Consider antiviral prophylaxis for herpes zoster reactivation.

- Consider prophylaxis for venous thromboembolism. For patients who are not at high risk for bleeding or VTE, either low-dose aspirin 81-100 mg PO daily or enoxaparin 40mg SC daily can be used.
- Careful consideration and monitoring must be taken with erythropoietin stimulating agents (ESAs), since the concomitant use of ESAs with lenalidomide may potentiate the risk of thrombosis.
- RBC or platelet transfusions with lenalidomide dose reductions/interruptions may be appropriate in severe / symptomatic anemia or thrombocytopenia.

Pre-medications for Daratumumab (subcut) (prophylaxis for administration-related reactions (ARRs)):

To be given at least 1 hour prior to each dose:

- Dexamethasone 20 mg IV/PO †
- Oral Antipyretic (e.g., acetaminophen 650-1000 mg)
- H1-receptor antagonist IV/PO (e.g., diphenhydramine 25-50 mg or equivalent)
- Montelukast 10 mg PO‡

†Dexamethasone on the day of injection may be given as part of pre-/post-medications for daratumumab; 20 mg IV/PO on the day of daratumumab injection and 20 mg PO on the day after injection. For patients receiving reduced dose dexamethasone 20 mg weekly, the entire 20 mg dose has been given prior to the daratumumab injection in some clinical trials.

‡Montelukast 10 mg was optional on Cycle 1 Day 1 during clinical trials of daratumumab (subcut). The addition of montelukast given prior to the first daratumumab IV infusion numerically reduced the incidence of respiratory infusion reactions in the study by Nooka et al.

Post-Injection Medications for Daratumumab (subcut) (prevention of delayed ARRs):

- Dexamethasone 20 mg PO for 1 day post-injection¶,§
- Consider bronchodilators (e.g., short and long acting) and inhaled corticosteroids (for patients with a history of COPD) ||, #

¶Dexamethasone on the day of injection may be given as part of pre-/post-medications for daratumumab; 20 mg IV/PO on the day of daratumumab infusion and 20 mg PO on the day after injection. For patients receiving reduced dose dexamethasone 20 mg weekly, the entire 20 mg dose has been given prior to the daratumumab injection in some clinical trials·

§May discontinue after the 3rd injection if no major systemic ARRs occurred (excluding regimen-specific corticosteroids).

||Consider adding an H1-receptor antagonist if the patient is at higher risk of respiratory complications.

#May be discontinued after the 4th injection if no major ARRs occurred.

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E - Dose Modifications

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

Women of child bearing potential must have two negative pregnancy tests before initiating lenalidomide treatment.

Assess risk of second primary malignancies prior to starting lenalidomide treatment.

Dosage with toxicity

Daratumumab dose reductions are not recommended. Doses were held for toxicity as suggested below and missed doses were not made up. Discontinue daratumumab if a dose is delayed by more than 28 days.

For lenalidomide, dose reductions were permitted at the following dose levels:

Dose level	Lenalidomide dose (mg)
0	25
-1	15
-2	10
-3	5
-4	Discontinue

Suggested dose modifications:

Toxicity	Daratumumab	Lenalidomide (counts x 10^9/L)
Thrombocytopenia	Hold* for grade 3 or higher thrombocytopenia with bleeding	Hold when platelet count first falls to < 30, monitor CBC weekly

		When count returns to ≥ 30, resume at one dose level reduction. For recurrence: Hold; when count returns to ≥ 30, resume at one dose level reduction.
Neutropenia	Hold* for grade 4 hematologic toxicity	Hold when ANC first falls to < 1, start G-CSF support, monitor CBC weekly. When count returns to ≥ 1 and neutropenia is only observed toxicity, resume at the previous dose. When count returns to ≥ 1 and other toxicity is observed, resume at one dose level reduction. For recurrence: Hold; when count returns to ≥ 1, resume at one dose level reduction.
Grade 2 or 3 rash	n/a	Hold or consider discontinuing.
Grade 4 skin rash, OR Exfoliative or bullous rash, OR Suspected Stevens-Johnson Syndrome, Toxic epidermal necrolysis or DRESS	Discontinue	
Increased LFTs	n/a	Hold and consider restarting at a lower dose when ≤ baseline.
Other Grade 3 or 4 non-hematologic toxicities**	Hold*	If related to lenalidomide, hold until ≤ grade 2. Resume at one dose level reduction.
Pneumonitis OR Progressive multifocal	Discontinue	

leukoencephalopathy	
Angioedema or anaphylaxis	Discontinue
Solid organ transplant rejection	Discontinue
HBV reactivation	Hold treatment (including steroids). Consult with a HBV expert and manage appropriately. Restart of treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

*Resume when toxicity has resolved to ≤ grade 2

**except for grade 3 nausea/vomiting responsive to antiemetics, grade 3 diarrhea responsive to antidiarrheals, isolated grade 3 GGT elevation or grade 3 fatigue for < 7 days post-infusion

Management of Daratumumab (subcut) Administration-Related 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 administration rate. • Manage the symptoms. **Restart:** • Consider restart if appropriate	• Consider rechallenge if appropriate.
3	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Consider restart if appropriate	• Consider rechallenge if appropriate.
4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Hepatic Impairment

For dexamethasone, no dosage adjustment is required.

Hepatic Impairment	Lenalidomide dose	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

For dexamethasone, no dosage adjustment is necessary.

Daratumumab is not renally cleared. For lenalidomide, clearance is decreased in renal impairment. The following dosage adjustments are suggested:

CrCl (mL/min)	Lenalidomide starting dose*	Daratumumab Dose
30-60	10 mg daily	No dose adjustment necessary
< 30 not requiring dialysis	15 mg every other day	
< 30 requiring dialysis	5 mg daily (after dialysis on dialysis days)	

*maintain day 1-21, q28 day schedule

Dosage in the Elderly

For daratumumab, no overall differences in efficacy was observed, but patients ≥ 65 years were more likely to experience serious adverse events (e.g., pneumonia) than those < 65 years.

For lenalidomide, the incidences of adverse events were significantly higher in patients over 65, including constipation, confusion, dyspnea, atrial fibrillation, diarrhea, fatigue, pulmonary embolism and syncope. This may be related to renal impairment. Monitor elderly patients closely and adjust the dose for renal impairment as suggested under "dosage with renal impairment".

Patients older than 75 or those with a BMI < 18.5 received dexamethasone at a reduced dose of 20 mg weekly in some clinical trials.

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F - Adverse Effects

Refer to daratumumab (subcut), dexamethasone, lenalidomide drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression +/- bleeding, infection (may be severe, including opportunistic infection, viral reactivation) • Diarrhea	• Edema • Constipation • Fatigue • Musculoskeletal pain • Nausea, vomiting • Cough, dyspnea	• Peripheral neuropathy • Anorexia, weight loss • Abnormal electrolytes • Dizziness • Headache • Rash (may be severe) • Tremor • Blurred vision • Systemic administration-related reactions (daratumumab subcut - may be severe) • Hypertension (may be severe) • Abdominal pain	• Arterial / venous thromboembolism • Arrhythmia • Cardiotoxicity • Hypotension • ↓Immunoglobulins • Nephrotoxicity • Hepatotoxicity • Pancreatitis • Cholecystitis • Secondary malignancy • Adrenal insufficiency • Hyper/hypothyroidism • Injection site reaction • Hypersensitivity • SJS, TEN • DRESS • Rhabdomyolysis • Hemolysis • PML • Tumour lysis syndrome • Pneumonitis

		• Dysgeusia • Corticosteroid effects (GI irritation, mood changes, hyperglycemia, insomnia)	• Corticosteroid effects (osteoporosis, cataracts) • Solid organ transplant rejection • GVHD

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G - Interactions

Refer to daratumumab (subcut), dexamethasone, lenalidomide drug monograph(s) for additional details

- Lenalidomide increases the concentration of digoxin. Use caution and monitor digoxin levels.
- Lenalidomide increases the risk of thromboembolism, and can have an additive effect with hormonal therapy, erythropoietic agents, and corticosteroids.
- Daratumumab interferes with 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. 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 (subcut), dexamethasone, lenalidomide drug monograph(s) for additional details

Administration

Daratumumab (subcut)

Daratumumab IV and subcutaneous formulations are **not interchangeable**. The dosing and

administration of these products are different.

- Daratumumab (subcut) does not require reconstitution or dilution.
- Compatible with polypropylene or polyethylene syringe material, polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets, and stainless steel transfer and injection needles.
- Administer by subcutaneous injection, over approximately 3-5 minutes.
- Inject into the abdominal wall only (approximately 7.5 cm to the right or left of the navel). Do not give in areas where the skin is red, bruised, tender, hard or where there are scars.
- If pain occurs during injection, pause or slow rate of injection. If pain is not improved, the remaining dose may be given at an alternate injection site (on the opposite side of the abdomen).
- If there are other subcutaneous medications, they should be given at separate sites.
- Do not shake vials.
- Store vials at 2-8°C. Bring vials to room temperature (15-30°C) before use. Keep out of direct sunlight.

Lenalidomide

- Drug available by outpatient prescription in pharmacy registered with a controlled distribution program.
- Swallow capsules whole; they should not be broken, chewed, or opened. Do not extensively handle the capsules.
- Administer capsules preferably with water, either with or without food. Do not remove from blister packs until ready to take the dose.
- Note: Females who could become pregnant, or who plan to become pregnant can handle lenalidomide capsules if they are using latex gloves.
- If a dose is missed, it may be taken up to 12 hours after the time it is normally taken. Otherwise, skip this and take the next dose on the following day at its usual scheduled time.
- Store capsules at room temperature (15 to 30°C).

Dexamethasone

- Oral tablets for self-administration

- Given with food, preferably in the morning
- Store tablets at room temperature

Contraindications

- Patients with a history of severe hypersensitivity to daratumumab or who have hypersensitivity to lenalidomide, pomalidomide, thalidomide or dexamethasone or who have hypersensitivity to any ingredients in the formulations or components of the containers.
- Pregnant or breastfeeding women.
- Women at risk of being pregnant and male patients who do not comply with contraception requirements.

Other Warnings/Precautions

- Daratumumab can cause severe administration-related reactions (ARRs), 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).
- Lenalidomide contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption
- Use with caution and consider venous thromboembolism prophylaxis when used in combination with corticosteroids or thrombogenic agents, such as hormones and erythropoietin (see adverse effects section)
- Exercise caution in patients with a history of venous thromboembolism or with risk factors for arterial thromboembolism (e.g. hypertension and hyperlipidemia), or risk factors for atrial fibrillation (e.g. electrolyte abnormalities, pre-existing heart disease, hypertension, infection).
- Use with caution in patients with high tumour burden; monitor closely and use appropriate precautions for tumour lysis syndrome.
- Use with caution and monitor closely in patients with previous viral infections such as HBV and herpes zoster.
- Lenalidomide may be associated with fatigue and dizziness; caution is required when driving or operating machinery.

Pregnancy and Lactation

- This regimen is contraindicated in pregnancy and in females and males of childbearing

potential who do not comply with the contraception conditions of lenalidomide's controlled distribution program. Refer to the controlled distribution program for full details.

- Breastfeeding is contraindicated.
- Fertility Effects:
  - Daratumumab: Unknown
  - Lenalidomide: Unlikely

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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 of daratumumab; if daratumumab is held, before each cycle of lenalidomide and as clinically indicated
- Blood; type and screen prior to starting daratumumab. In the event of a planned transfusion, notify blood transfusion centres.
- Liver function tests; Baseline, at each visit, and as clinically indicated
- Renal function tests and electrolytes; Baseline, at each visit, and as clinically indicated
- Thyroid function tests; Baseline and as clinically indicated
- Pregnancy testing requirements for women of child-bearing potential; Before starting and as 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
- Cancer screening for occurrence of second primary malignancy; Assess risk prior to starting treatment; then at each visit or as clinically indicated
- Clinical toxicity assessments of systemic administration-related or injection site reactions with daratumumab, hypersensitivity, cardiac, neurologic and respiratory symptoms, rash, diarrhea, fatigue, constipation, infection (including viral

reactivation), anemia, bleeding, tumour lysis syndrome, thromboembolism; At each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- ECG; Baseline; repeat if arrhythmia suspected
- INR in patients receiving warfarin; Baseline and as clinically indicated

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J - Administrative Information

Dexamethasone and lenalidomide: outpatient prescriptions for home administration

Daratumumab (SC):

Approximate Patient Visit	1.5 hours
Pharmacy Workload (average time per visit)	17.650 minutes
Nursing Workload (average time per visit)	42.333 minutes

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K - References

Daratumumab (subcut) and lenalidomide drug monographs, Cancer Care Ontario.

Dimopoulos MA, Oriol A, Nahi H, et al; POLLUX Investigators. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Oct 6;375(14):1319-1331.

Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019 May 30;380(22):2104-15.

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.

pCODR expert review committee final recommendation: daratumumab (with lenalidomide and dexamethasone in newly diagnosed multiple myeloma). March 5, 2020.

PEBC Advice Documents or Guidelines

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

September 2022 Changed Lenalidomide to ODB LU

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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.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

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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