Written By: Lauren Trisler, PharmD, BCOP
Institution: Carle Cancer Center

Daratumumab for the Management of Multiple Myeloma

Description: The purpose of this document is to provide clinical guidance for optimal administration of daratumumab in the management of patients with multiple myeloma.

Background: Daratumumab is a human IgG1κ monoclonal antibody directed against CD38, a cell surface protein highly expressed on multiple myeloma cells. Binding to CD38 triggers immune-mediated tumor cell death and apoptosis. It is available as an intravenous (IV) formulation (Darzalex®) and a fixed-dose subcutaneous (SC) injection containing hyaluronidase (Darzalex Faspro®).

FDA Indications:

- Daratumumab is indicated for the treatment of adult patients with multiple myeloma as monotherapy or in combination with FDA-approved backbone regimens in newly diagnosed (transplant-eligible and transplant-ineligible) and relapsed/refractory settings. Approved regimens, line-of-therapy requirements, and treatment settings vary by formulation; see prescribing information (PI) for complete details.
- **Note:** The SC formulation has additional indications, including high-risk smoldering multiple myeloma and newly diagnosed light chain amyloidosis.

Most common adverse reactions (≥ 20%):

- Hematologic: neutropenia, thrombocytopenia, anemia
- Infections: primarily upper respiratory tract infections
- Infusion-related reactions (IRRs), more common with IV administration
    - IV: 37% during Week 1; incidence decreases with subsequent infusions
    - SC: ~ 13% overall; injection-site reactions may occur
- Gastrointestinal: diarrhea, constipation, nausea
- General: fatigue, asthenia, pyrexia, peripheral edema
- Respiratory: cough and dyspnea
- Peripheral sensory neuropathy

PQI Process:

**Unless otherwise specified, guidance applies to IV daratumumab. The SC formulation is administered as a fixed-dose injection and does not require infusion titration, dilution, or in-line filtration.*

Prior to Initiation (Week 1):

- Confirm correct formulation at order entry
- Verify dose and schedule:
    - IV: 16 mg/kg (actual body weight)
    - SC: 1,800 mg daratumumab / 30,000 units hyaluronidase (flat dose) SC into the abdomen over ~ 3-5 minutes[2]. Rotate injection sites.
- Standard schedule (monotherapy and lenalidomide- or pomalidomide-dexamethasone combinations):

    - Weeks 1-8: weekly
    - Weeks 9-24: every 2 weeks
    - Weeks 25+: every 4 weeks until disease progression or unacceptable toxicity
    - ***Note: schedules vary by regimen; refer to PI or protocol for details***
- Review concomitant medications and infusion parameters (rates, duration, dilution volumes)
- Determine whether Day 1 daratumumab will be administered as a single dose or split dose
    - Split dosing may be considered if full infusion cannot be completed as a single dose due to volume restrictions, etc.
- Ensure premedications are ordered (to be given 1-3 hours prior)[1] – IV and SC formulations
    - Corticosteroid:
        - Monotherapy: methylprednisolone 100 mg IV (or equivalent corticosteroid; may reduce to 60 mg after the 2nd infusion)
        - Combination: dexamethasone 20 mg PO/IV; if dexamethasone is part of the treatment regimen, that dose serves as the premedication
    - Acetaminophen 650-1000 mg PO
    - Diphenhydramine 25-50 mg PO/IV
    - Consider adding montelukast[3] and/or famotidine for first 2-3 infusions
- Ensure post-infusion corticosteroids are ordered to reduce risk of delayed IRRs
    - Monotherapy: methylprednisolone 20 mg PO (or equivalent corticosteroid) for 2 days starting the day after infusion
    - Combination: consider methylprednisolone ≤ 20 mg PO beginning the day after infusion; if background steroid is given that same day, additional corticosteroids may not be needed
    - SC formulation only: if no major systemic reactions after first 3 doses, consider discontinuing post-dose corticosteroids (excluding background regimen steroids)
- Consider bronchodilators/inhaled corticosteroids in patients with chronic obstructive pulmonary disease (may discontinue after 4 doses if no major reactions)
- Initiate herpes zoster prophylaxis within 1 week of starting therapy; continue for 3 months after completion.
- Screen for hepatitis B virus prior to initiation and monitor for reactivation.
- Notify blood banks prior to initiation, as daratumumab may interfere with indirect antiglobulin testing and blood compatibility testing
    - Obtain a baseline type and screen prior to first dose
    - Provide the patient with a wallet card documenting blood type and antibody screen status
- Prior to preparation, confirm vial labels match intended formulation
- IV administration requires in-line PES filter (0.22–0.2 micron); do not co-infuse with other medications
- Monitor for infusion-related reactions (IV), injection-site reactions (SC), and systemic hypersensitivity reactions (particularly after the first dose).
- Patients with Grade 1-3 reactions may be rechallenged
    - Permanently discontinue for the 3rd occurrence of Grade 3 or any Grade 4 reaction

<u>Prior to Week 2</u>

- Assess for prior infusion-related reaction:
    - If none: use a dilution volume of 500 mL; follow Week 2 titration schedule
    - If reaction occurred: use a dilution volume of 1,000 mL
- Monitor CBC for neutropenia and thrombocytopenia regularly during treatment

<u>Week 3 and beyond (IV formulation only)</u>

- If prior reaction occurred, resume at prior tolerated rate per protocol
    - If no Week 2 reaction, 90-minute infusion may be considered[4]
        - Monitor vital signs during rapid infusion and observe for 30 minutes post-infusion

Patient-Centered Activities:

- Review the planned treatment schedule with the patient and supply a treatment calendar and daratumumab Patient Education Sheet
    - Issue a wallet card documenting blood type and antibody screen status and instruct patient to carry it throughout treatment and for at least 6 months after completion
- Counsel patient on disease state, treatment regimen, and potential adverse reactions; verify understanding
- Educate patient on the risk of hepatitis B virus reactivation and the importance of adherence to prescribed antiviral prophylaxis for herpes zoster prevention

References:

1. Darzalex® (daratumumab) [PI].
2. Darzalex Faspro® (daratumumab and hyaluronidase-fihj) [PI].
3. Chari A, Mark TM, Krishnan A, et al. Use of montelukast to reduce infusion reactions in an early access treatment protocol of daratumumab in United States patients with relapsed or refractory multiple myeloma. Blood. 2016;128(22):2142.
4. Barr H, Dempsey J, Waller A, et al. Ninety-minute daratumumab infusion is safe in multiple myeloma. Leukemia 32, 2495–2518 (2018). https://doi.org/10.1038/s41375-018-0120-2.

Supplemental Information:
Infusion rates, duration, and dilution volumes for daratumumab administrations[1,4]

	Dilution Volume	Initial Rate (1st hour)	Rate Increment (absence of reaction)	Maximum rate	Average Infusion Duration
Week 1					
Option 1: Single Dose (16 mg/kg)	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour	7 hours
Option 2 Split Dose: Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour	4.2 hours
Option 2 Split Dose: Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour	4.2 hours
Week 2 (16mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour	4 hours
Week 3 & Beyond (16mg/kg)					
Option 1: Standard Infusion	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour	3 hours
Option 2: 90 Minute Infusion	500 mL	200 mL/hour for 30 minutes (20% of dose)		450 mL/hour over 60 minutes (80% of dose)	90 minutes