Daratumumab (DARZALEX™)

Description and Pharmacology: Daratumumab is an IgG1κ human monoclonal antibody that binds to CD38, a cell surface glycoprotein that is uniformly overexpressed on myeloma cells. Daratumumab induces direct tumor cell apoptosis, through Fc mediated cross-linking, as well as immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP).

Pharmacokinetics: Metabolism: None. Distribution: Central (4.7 ± 1.3 L). Half-life: 18 ± 9 days.

Indication & Usage: Monotherapy for 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 or who are double-refractory to a PI and an immunomodulatory agent.

Contraindications: None.

Warnings & Precautions:

- Infusion reactions were reported in approximately 50% of patients in clinical trials and severe infusion reactions (including bronchospasm, hypoxia, dyspnea, and hypertension) may occur, mostly during the first infusion. Reactions may also be seen during subsequent infusions, generally during the infusion or within 4 hours of completion (median onset: 1.5 hours); some reactions occurred up to 48 hours after the infusion. Premedication with antihistamines, antipyretics, and corticosteroids is required. Administer in a facility with immediate access to resuscitative measures (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen). Administer oral corticosteroids on the first and second day after infusion to reduce risk of delayed infusion reactions. Consider short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders; monitor closely.
- Bone marrow suppression: lymphopenia, neutropenia, thrombocytopenia, and anemia, including grade 3 and 4 toxicities, were commonly reported as treatment emergent adverse reactions in clinical trials. Monitor complete blood counts as clinically necessary.
- Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting the assessment of complete responses (by IMWG criteria).
- Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Use may result in a positive indirect antiglobulin test (Coombs test) for up to 6 months after the last infusion; ABO and Rh blood type determination are not affected. Type and screen patients prior to therapy initiation.
- Females of reproduction potential should use effective contraception during therapy and for 3 months after treatment is complete.
- Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of daratumumab. Systemic antivirals were used in 73% of patients. Herpes zoster reported in 3% of patients. Initiate antiviral prophylaxis within 1 week of starting daratumumab and continue for 3 months after cessation of daratumumab treatment.

Drug/food interactions: None.

Major adverse effects:

- Most frequently reported adverse reactions (incidence >20%): infusion reactions, fatigue, nausea, back pain, pyrexia, cough, upper respiratory infection

    - Infusion site reactions (first infusion: 48%; grade 3: 3%; second: 5%; subsequent: 4%)
- Most frequently reported lab abnormalities: lymphocytopenia (72%; grade 3: 30%; grade 4 (10%), neutropenia (60%; grade 3: 17%; grade 4: 3%, thrombocytopenia (48%; grade 3: 10%; grade 4: 8%), anemia (45%; grade 3: 19%)

Clinical trials: A phase 1-2, two-part, open-label, multicenter trial was conducted to evaluate the safety and efficacy of DARZALEX monotherapy in 106 patients with relapsed myeloma or relapsed myeloma that was refractory to two or more prior lines of therapy. Part 1 was an 8 week long dose-escalation study that assessed safety and pharmacokinetics. In part 2, dose of daratumumab of 8 mg/kg and 16 mg/kg were administered with different schedules and patients received therapy until disease progression or an unmanageable level of toxic events occurred. The NCI Common Terminology Criteria for Adverse Events were used for the primary endpoint of safety assessment. Secondary endpoints were PK, objective response according to IMWG uniform response criteria for myeloma, relative reductions in levels of M protein and free light chains, time to disease progression, duration of response, progression-free survival, and overall survival.

In part 1 (32 patients), single dose-limiting toxic events were observed at doses of 0.1 mg/kg and 1 mg/kg. In part 2 (72 patients), the median time since diagnosis was 5.7 years and patients had received a median of four prior therapies; 79% of the patients had disease that was refractory to the last therapy received (64% refractory to bortezomib and lenalidomide), 76% had received autologous stem-cell transplants.

There was no maximum tolerated dose identified in part 1. In part 2, infusion-related reactions were mild (71% of patients had an event of any grade, 1% had grade 3 event), with no dose-dependent adverse events. The most common adverse events of grade 3 or 4 ($\geq$ 5% of patients) were pneumonia and thrombocytopenia. In the cohort that received 16 mg/kg, the overall response rate was 36% (15 patients had a partial response or better, 2 had a complete response), the median progression-free survival was 5.6 months (95% CI, 4.2 to 8.1), and 65% (95% CI, 28 to 86) of the patients who had a response did not have progression at 12 months.

Dosage & Administration:
Dose (IV): 16 mg/kg (based on actual body weight) given once weekly in Weeks 1 to 8, once every 2 weeks in Weeks 9 to 24, once every 4 weeks in Weeks 25 and beyond until disease progression or unmanageable toxicity. If a dose is missed, give as soon as possible and adjust schedule (maintain treatment interval).

Premedication with an IV corticosteroid and PO antipyretic and IV or PO antihistamine is required.

Approximately 60 minutes prior to infusion: IV methylprednisolone 100 mg or equivalent (dose may be decreased after second infusion; eg, 60 mg methylprednisolone) *plus* PO acetaminophen 650-1000 mg *plus* IV or PO 25-50 mg diphenhydramine.

On day 1 and 2 after each infusion: oral corticosteroid (eg, methylprednisolone 20 mg or equivalent)

Administer with an infusion set fitted with a flow regulator and with an inline, sterile, non-pyrogenic, low protein-binding polyether sulfone filter (0.22 or 0.2 micrometer). Polyurethane, polybutadiene, polyvinylchloride, polypropylene, or polyethylene administration sets are required. Begin infusion immediately after infusion bag reaches room temperature (if refrigerated). Infusion should be administered within 15 hours. Discard any unused portion.

Infusion Rate:

	Dilution Volume	*Initial rate (first hour)*	*Rate Increment*	*Maximum rate*
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion [A]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions [B]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

A: Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.
B: Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions.

Dosing Adjustments:
Renal/Hepatic: No dosage adjustment necessary for renal impairment or mild hepatic impairment. Daratumumab has not been studied in patients with moderate to severe hepatic impairment.

Infusion reactions: Immediately interrupt infusion for reaction of any severity and manage symptoms as clinically appropriate (eg, antihistamines, NSAIDs, glucocorticoids).

Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated	Severe but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling	Life-threatening consequences; urgent intervention indicated

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, NIH, National Cancer Institute.

Grade 1 or 2 infusion reaction: Once symptoms resolve, resume infusion at no more than 50% of rate at which reaction occurred. If no further reactions are observed, may escalate infusion rate as appropriate.
Grade 3 infusion reaction: If symptoms improve to grade 2 or lower, consider resuming infusion at no more than 50% of rate at which reaction occurred. If no further reactions are observed, may escalate infusion rate as appropriate. If a grade 3 reaction recurs, repeat the steps above. Permanently discontinue if a grade 3 infusion reaction occurs for the third time.
Grade 4 infusion reaction: Permanently discontinue.

Preparation: DARZALEX solution is colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required, and number of vials needed based on patient's actual body weight.
- Using aseptic technique, remove a volume of 0.9% Sodium Chloride Injection, USP from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZELAX solution and dilute to the appropriate volume by adding to the infusion bag/container containing 0.9% Sodium Chloride Injection, USP.
- Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Following dilution the infusion bag/container may be stored for up to 24 hours in a refrigerator at 2ºC to 8ºC (36F to 46F), protected from light. Do not freeze.

Compatibilities: NS

Patient monitoring: Complete blood cell counts before every infusion; type and screen (blood type) prior to initiating therapy; signs/symptoms of infusion reactions.

Medication safety:
Pregnancy category D.

Sound-alike/look-alike issues: Daratumumab may be confused with dinutuximab.

High alert medication: This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Cost and availability: Solution (Darzalex Intravenous) 100 mg/5 mL (5 mL): $540.00; 400 mg/20 mL (20 mL): $2160.00

Recommendations: Addition to formulary as single-agent for treatment of relapsed/refractory myeloma.

References

Daratumumab. In: Lexi-Drugs [database on the Internet]. Hudson (OH): Lexi-Comp, Inc.; 2007 [cited 2016 Feb 4].

Daratumumab [package insert]. Horsham (PA): Janssen Biotech, Inc; 2015.

Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. New Engl J Med. 2015; 373(13): 1207-1219.