Regimen Protocols

Dara-LD: Daratumumab/Lenalidomide/Dexamethasone

Constituents of Regimen: daratumumab, lenalidomide and dexamethasone

Common Names or Abbreviations for Regimen: DARA + LEN/DEX, Dara-LD

Other Names of Regimen Constituents:

- Daratumumab: Darzalex®
- Lenalidomide: Revlimid®, CC-5013, CC5013, CDC 501, IMID-1
- Dexamethasone: Aeroseb-Dex, Decaderm, Decadron®, DM, DXM

Mechanism of Action:

CD38, a transmembrane glycoprotein expressed on the surface of hematopoietic cells, including myeloma cells, functions in receptor mediated adhesion, signaling and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and induces apoptosis in myeloma cells through Fc-mediated cross linking and immune-mediated tumor cell lysis via complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP).[1]

U.S. FDA-Approved Indication(s):

Daratumumab is indicated 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 double-refractory to a PI and an IMiD.

NCCN Recommended Indication:

Daratumumab is recommended for previously treated multiple myeloma in patients who have received at least three prior lines of therapy including a PI and an IMiD or who are double-refractory to a PI and an IMiD.

NCCN Preferred Regimen or Other[2]: Other, for previously treated multiple myeloma

NCCN Category of Evidence[2]: 2A

Dose Schedule:

Relapsed/Refractory Disease Phase I/II Protocol Dose Schedule [28-day cycle][3]:

- Daratumumab 16 mg/kg IV once weekly during cycles 1-2, once every other week during cycles 3-6, then once monthly in cycles 7+
- Lenalidomide 25 mg PO days 1-21 of each cycle
- Dexamethasone 40 mg PO once weekly

Primary and Secondary Efficacy Outcomes:

Safety and Efficacy of Daratumumab with Lenalidomide and Dexamethasone in Relapsed or Relapsed, Refractory Multiple Myeloma[4]

- 15/20 patients achieved PR or better, 3/20 with CR, 6/20 with VGPR.
- Median time to response was 4.3 weeks (range: 2.1-11.3).
- Overall response rate (ORR) was 75% (15/20) combining all patients in part 1 and 2 and 92.3% (12/13) for part 1 patients who had at least 2 months of follow-up or discontinued earlier.

Daratumumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed or Relapsed and Refractory Multiple Myeloma: Updated Results of a Phase 1/2 Study (GEN503)[3]

- At data cut-off (1/9/2015), the following efficacy endpoints were met for patients in the expansion cohort (n=32) receiving DARA + LEN/DEX:
  - Overall response rate (ORR) was 88%, with 11 (34%) partial responses (PR) and 17 (53%) ≥ very good partial responses (VGPR) that included 7 (22%) stringent complete responses (sCR), 1 (3%) complete response (CR), and 9 (28%) VGPRs
  - Median time to first response was 1 month (95% CI, 0.9-1.9)
  - Median time to best response was 4.5 months (95% CI, 1.9-5.6)

Safety:

Daratumumab General Safety[1]:

- Infusion Reactions (IRs): approximately half of all patients experience an IR, with most during the first infusion, but IRs can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing the infusion; prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.
  - Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, and hypertension.
  - Signs and symptoms may include respiratory symptoms, such as cough, wheezing, larynx and throat tightness and irritation, laryngeal edema, pulmonary edema, nasal congestion, and allergic rhinitis.
  - Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills.
- Interference with Serological Testing: daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (Coombs test). A daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum.

- Interference with Determination of Complete Response: daratumumab can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Safety and Efficacy of Daratumumab with Lenalidomide and Dexamethasone in Relapsed or Relapsed/Refractory Multiple Myeloma[4]

- Most frequent (>30% patients) adverse events (AEs) were neutropenia and diarrhea; no dose limiting toxicities (DLTs) were reported.
- Infusion reactions (Grade 1 and 2) were reported in 4 patients.

Daratumumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma: Updated Results of a Phase 1/2 Study (GEN503)[3]

- Most common (>25%) treatment-emergent AEs (TEAEs) included neutropenia (81%), muscle spasms (44%), cough (38%), diarrhea (34%), fatigue and hypertension (28% each)
- Neutropenia was the most frequently (>25%) reported Grade 3 or 4 TEAEs (75%)
- One (3%) patient experienced febrile neutropenia (Grade 1)
- Eighteen (56%) patients had infusion reactions (IRs) and these were generally mild to moderate and occurred mostly during the first cycle
    - IRs included cough (25%), allergic rhinitis, nausea, and vomiting (9% each), as well as dyspnea, nasal congestion, and hypertension (6% each)
    - Two (6%) patients had Grade 3 IRs (laryngeal edema and hypertension)

Lenalidomide General Safety[5]:

Black box warning

- Embryo-Fetal Toxicity: caused limb abnormalities in a developmental monkey study. In females of reproductive potential, obtain 2 negative pregnancy tests before starting lenalidomide .
- Hematologic Toxicity (Neutropenia and Thrombocytopenia): patients should have blood counts monitored and may require dose interruptions and/or reductions, in addition to blood product support and/or growth factors
- Venous and Arterial Thromboembolism: increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma. Thromboprophylaxis is recommended and the choice of regimen should be based on the patient's underlying risks.

- Second Primary Malignancies: patients with multiple myeloma who are treated with lenalidomide have an increased risk of developing acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS)
- Hepatotoxicity: hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. Preexisting viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors.
- Allergic Reactions: Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported.
- Tumor Lysis Syndrome: patients with higher tumor burden are at increased risk.
- Impaired Stem Cell Mobilization: a decrease in the number of CD34+ cells collected after treatment (>4 cycles) with lenalidomide has been reported. In patients who are stem cell transplant candidates, referral to a transplant center should occur early in treatment to optimize the timing of the stem cell collection.

Required Supportive Care/Prophylaxis:

- To decrease the risk of infusion reactions, a pre-infusion (administered **1 hour before** daratumumab infusion) and post-infusion concomitant medication regimen is recommended[1]:
    - Pre-Infusion: methylprednisolone 100 mg IV, or equivalent dose of an intermediate-acting or long-acting corticosteroid; acetaminophen 650 to 1000 mg PO; diphenhydramine 25 to 50 mg or equivalent IV or PO
        - After the second infusion, methylprednisolone may be dose-reduced to 60 mg IV
    - Post-Infusion: methylprednisolone 20 mg PO or equivalent dose of a corticosteroid on the first and second day after all infusions
        - For patients with a history of obstructive pulmonary disorder, consider bronchodilators and inhaled corticosteroids post-infusion
- Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting daratumumab and continue for 3 months following treatment.[1]
- Multiple myeloma (MM) is an inherently hypercoagulable disease. Patients who receive immunomodulatory containing regimens are at an increased risk for venous thromboembolic events. Thus, anticoagulation is advised in patients receiving immunomodulatory drug regimens, due to the high incidence of venous thrombosis observed.[6]
- Pneumococcal infections are common in patients with multiple myeloma. Pneumococcal vaccination should be completed at the time of diagnosis and repeated in 5 years to minimize preventable illness.[7]

- Bisphosphonates (zoledronic acid or pamidronate) are intended to decrease the risk of skeletal-related events and should be considered in all patients with MM receiving first-line therapy and throughout the disease, regardless of presence of osteolytic bone lesions on conventional radiography. Dental health should be evaluated at baseline and an ongoing basis to assess for osteonecrosis of the jaw. Serum creatinine levels should be obtained prior to each bisphosphonate dose. Periodic 24-hour urine monitoring should be performed to assess for renal damage secondary to bisphosphonate use long-term.[8]

Tailoring of Regimen:

- Infusion Reactions: For IRs of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms.[1]
    - Grade 1 -2 IR: Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate
    - Grade 3 IR: if the intensity of the reaction decreases to Grade 2 or lower, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined below.
        - Repeat the procedure above in the event of recurrence of Grade 3 symptoms.
        - Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.
    - Grade 4 IR: permanently discontinue daratumumab

Infusion rates for administration of daratumumab

	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.

- Renal Impairment: Daratumumab requires no dosage adjustment for patients with pre-existing renal impairment.[1] Lenalidomide is primarily excreted unchanged by the kidney, so dose-adjustments are recommended in patients with renal dysfunction as follows[5]:

Category	Renal Function (Cockcroft-Gault)	Dose in MM
Moderate Renal Impairment	CLcr 30-50 mL/min	10 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.

- Hepatic Impairment: Daratumumab requires no dosage adjustment for patients with mild hepatic impairment (total bilirubin [TB] 1.0×-1.5× ULN or aspartate aminotransferase [AST] > ULN).[1] Lenalidomide has not been studied in patients with hepatic impairment, but it is primarily excreted unchanged by the kidney.[5]
    - Daratumumab has not been studied in patients with moderate to severe hepatic impairment (TB >1.5× ULN and any AST)
- Hematologic Toxicities: Lenalidomide should be dose-adjusted based on reductions in platelets and absolute neutrophil counts:

Platelet counts

Thrombocytopenia in MM

When Platelets	Recommended Course
Fall to <30,000/mcL	Interrupt REVLIMID treatment, follow CBC weekly
Return to ≥30,000/mcL	Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <30,000/mcL	Interrupt REVLIMID treatment
Return to ≥30,000/mcL	Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily

Absolute Neutrophil counts (ANC)

Neutropenia in MM

When Neutrophils	Recommended Course
Fall to <1000/mcL	Interrupt REVLIMID treatment, follow CBC weekly
Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume REVLIMID at 25 mg daily or initial starting dose
Return to ≥1,000/mcL and if other toxicity	Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <1,000/mcL	Interrupt REVLIMID treatment
Return to ≥1,000/mcL	Resume REVLIMID at next lower dose. Do not dose below 2.5 mg daily

Strategies to Reduce Treatment-associated Side Effects:

- Administer the pre-infusion and post-infusion medications to decrease the risk of infusion reactions, as outlined above [See ***"Required Supportive Care/Prophylaxis"***][1]
- A CBC with differential should be obtained to monitor neutropenia and thrombocytopenia and intervene (with dose reduction, discontinuation of the causative agent) if necessary.
- Standard aspirin or LMWH prophylaxis is recommended for patients receiving lenalidomide-containing regimens. Regular physical activity should be encouraged to combat muscle weakness and prevent VTEs.[6]
- Corticosteroids such as dexamethasone can lead to many side effects such as hyperglycemia, mood swings, insomnia, and proximal muscle weakness. Prior to starting a corticosteroid-containing regimen, patients should be screened for a history of diabetes, mood disorders, and psychiatric illnesses.[9]

Monitoring Recommendations and Notes:

Adverse events [as listed above under ***"Safety"***] should be monitored for and addressed at each visit.[1,2,5]

- Regular CBC/diff and chemistry monitoring to assess for hepato/renal abnormalities, myelosuppression is recommended.
- Patients should be educated regarding the side effects of medications as listed above, especially signs of thrombocytopenia, infection, cardiac toxicity, allergic and

dermatologic reactions, and urged to report side effects to providers.

- Objective monitoring of responses to the regimen should be performed on a monthly basis (by IMWG Uniform Response Criteria) and recorded.

References:

1. Darzalex® [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2015.
2. National Comprehensive Cancer Network [NCCN]. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Multiple Myeloma. Version 3.2016.
3. Plesner T, Arkenau H-T, Gimsing P, et al. Daratumumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed or Relapsed and Refractory Multiple Myeloma: Updated Results of a Phase 1/2 Study (GEN503). In: 57th American Society of Hematology Annual Meeting and Exposition; Dec 5-8, 2015; Orlando, FL. Abstract 507.
4. Plesner T, Arkenau H-T, Lokhorst HM, et al. Safety and Efficacy of Daratumumab with Lenalidomide and Dexamethasone in Relapsed or Relapsed, Refractory Multiple Myeloma. In: 56th American Society of Hematology Annual Meeting and Exposition; Dec 6-9, 2014; San Francisco, CA. Abstract 84.
5. Revlimid® [prescribing information]. Summit NJ: Celgene Corporation; 2015.
6. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008;22(2):414-423.
7. Prevention of pneumococcal disease: Recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*. 2014;46:1-24.
8. Terpos E, Roodman GD, Dimopoulos MA. Optimal use of bisphosphonates in patients with multiple myeloma. *Blood*. 2013;121(17):3325-3328.
9. Faiman B, Bilotti E, Mangan P, et al. Steroid-Associated Side Effects in Patients With Multiple Myeloma: Consensus Statement of the IMF Nurse Leadership Board. *Clin J Oncol Nurs*. 2008;12(0):53-62.

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