Darzalex (Daratumumab) Approved as Part of a 3-Drug Regimen for Patients with Multiple Myeloma

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Multiple myeloma is a cancer of plasma cells in the bone marrow that often leads to bone destruction and bone marrow failure.1,2 Representing approximately 1% of all cancers, multiple myeloma is the second most common hematologic malignancy after non-Hodgkin lymphoma.3 According to the American Cancer Society, an estimated 30,280 new cases of multiple myeloma will be diagnosed in 2017, and 12,590 people will die from this disease.4 The complications of multiple myeloma include back pain, kidney dysfunction, bone loss, impaired immunity, and anemia.5

Immunomodulatory drugs (IMiDs) and proteasome inhibitors represent the cornerstones of initial treatment for multiple myeloma.2,6 Treatment options have recently expanded for patients with relapsed disease. In November 2015, the US Food and Drug Administration (FDA) approved 3 new agents for the treatment of relapsed multiple myeloma.7

Novel agents for multiple myeloma have had a considerable impact on the healthcare budget. Two evaluations of the economics of novel agents for multiple myeloma showed that the use of bortezomib (Velcade) or bortezomib-based therapy was more cost-effective than the use of IMiDs in combination with other multiple myeloma agents.8,9

Mechanism of Action
Daratumumab is an immunoglobulin (Ig) G1 kappa human monoclonal antibody that targets CD38 and inhibits the growth of CD38-expressing tumor cells by inducing apoptosis directly, as well as by immune-mediated tumor-cell lysis.10

Dosing and Administration
The recommended dose of daratumumab is 16 mg/kg of body weight administered as an intravenous infusion. When used in combination with Rd (DRd), daratumumab is dosed weekly in weeks 1 to 8, every 2 weeks in weeks 9 to 24, and every 4 weeks until disease progression beginning with week 25.10 When used in combination with Vd (DVd), daratumumab is dosed weekly in weeks 1 to 9, every 3 weeks in weeks 10 to 24, and every 4 weeks until disease progression beginning in week 25.10 Dose reductions of daratumumab are not recommended.10

Patients who receive daratumumab should be premedicated with corticosteroids, antipyretics, and antihistamines. Patients should also receive corticosteroids on the first and second day after each daratumumab infusion. Antiviral prophylaxis should be initiated after 1 week of starting daratumumab and continued for 3 months after treatment.10

Daratatumab Distribution
Daratumumab can be accessed through several networks and specialty pharmacies, including ASD Healthcare, Cardinal Health Specialty Pharmaceutical Distribution, CuraScript Specialty Distribution (Priority Healthcare), McKesson Plasma and Biologics, McKesson Specialty Health, and Oncology Supply.15

The 2 Pivotal Clinical Trials
The POLLUX Study
Overall, 569 patients with relapsed or refractory multiple myeloma enrolled in the open-label POLLUX study that compared the efficacy and safety of DRd with that of Rd.10,12 Daratumumab (16 mg/kg intravenously) was administered with preinfusion and postinfusion medications until unacceptable toxicity or until disease progression.10 Lenalidomide 25 mg once daily was administered on days...
1 to 21 of each 28-day cycle. Dexamethasone 40 mg or 20 mg was dosed each week based on age and on body mass index. The primary end point was PFS.

The majority of patients were male (59%) and white (69%), and had received a median of 1 previous therapy, including autologous stem-cell transplantation (ASCT) in 63% of patients.

The median PFS was not reached in the DRd arm compared with 18.4 months in the Rd arm (hazard ratio [HR], 0.37; 95% confidence interval [CI], 0.27-0.52; P <.0001), representing a 63% reduction in the risk for disease progression or death in patients who received DRd. The overall response rate (ORR) associated with DRd was 91%, which included 18% stringent complete responses, 25% complete responses, 32% very good partial responses, and 17% partial responses (Table).

**The CASTOR Study**

This open-label study included 498 patients with relapsed or refractory multiple myeloma and compared the efficacy and safety of DVd and Vd. Daratumumab (16 mg/kg) was administered with preinfusion and postinfusion medications until unacceptable toxicity or until disease progression. Bortezombib was administered by subcutaneous injection or intravenously at 1.3 mg/m² of body surface area twice weekly for 2 weeks of repeated 21-day cycles, for a total of 8 cycles. Dexamethasone was dosed based on the patient’s age and body mass index. The primary end point was PFS.

The majority of patients enrolled in the CASTOR study had received a median of 2 previous therapies, including ASCT in 61% of patients.

The median PFS was not reached in the DVd arm versus 7.2 months in the Vd arm (HR, 0.39; 95% CI, 0.28-0.53; P <.0001). The risk for disease progression or death was reduced by 61% in patients who received DVd. The ORR associated with DVd was 79%, which included 4% stringent complete response, 14% complete response, 38% very good partial response, and 23% partial response.

**Adverse Events**

A total of 286 patients in the POLLUX study received DRd for a median of 13 months (range, 0-21 months). Adverse events that occurred in ≥20% of patients who received DVd included infusion reactions (45%), diarrhea (32%), peripheral edema (22%), upper respiratory tract infection (44%), peripheral sensory neuropathy (47%), cough (27%), and dyspnea (21%). Serious adverse events were 42% with DVd versus 34% with Vd. Adverse events led to discontinuation of therapy in 7% of DVd recipients versus 9% of Vd recipients.

**Warnings and Precautions**

Daratumumab infusion should be interrupted for reactions of any severity. Treatment should be permanently discontinued for life-threatening (grade 4) reactions. Patients with grade 1, 2, or 3 reactions should receive daratumumab at a reduced infusion rate when restarting therapy.

Daratumumab binds to CD38 on red blood cells, resulting in a positive indirect antiglobulin test or Coombs test that can persist for up to 6 months after the last infusion. Patients’ blood should be typed and screened before starting daratumumab therapy.

Daratumumab can increase neutropenia and thrombocytopenia that are induced by other therapies. Daratumumab dose delay may facilitate neutrophil and/or platelet recovery. Dose reduction of daratumumab is not recommended.

Daratumumab can be detected on serum protein electrophoresis and immunofixation assays that are used to monitor endogenous M-protein. This can affect the determination of complete response and disease relapse after complete response in patients with IgG kappa myeloma protein.

**Use in Specific Populations**

There are no human data to inform the risk for birth
defects with daratumumab therapy during pregnancy. The benefits of breast-feeding should be considered in addition to the mother's need for daratumumab and any potential adverse effects of daratumumab on the breast-fed child.

Women of reproductive potential should use effective contraception during treatment and for 3 months after stopping daratumumab therapy.

The safety and effectiveness of daratumumab in pediatric patients have not been established; no overall differences were observed between patients aged ≥75 years and younger patients.

Conclusion
Daratumumab, a monoclonal antibody that targets CD38, has demonstrated efficacy in combination with Rd or Vd in patients with previously treated multiple myeloma. Two large clinical trials showed that daratumumab-based combination regimens reduce the risk for disease progression or death in patients with multiple myeloma.

References