FDA Approves Darzalex Combo for Newly Diagnosed Multiple Myeloma

Four-drug regimen improves response in people being treated for the first time.

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The Food and Drug Administration (FDA) this week added a new approval for the monoclonal antibody Darzalex (daratumumab) for use in a combination regimen as first-line therapy for people newly diagnosed with multiple myeloma.

Approval was supported by a Phase III study that showed that adding Darzalex to Velcade (bortezomib), melphalan and prednisone improved progression-free survival, meaning patients were still alive without disease progression, and nearly doubled the complete response rate for people with newly diagnosed disease.

Multiple myeloma involves uncontrolled growth of plasma cells, a type of B cell that produces antibodies. These malignant cells multiply in the bone marrow and can clump together to form tumors. Excess myeloma cells may interfere with cells that repair bone, leading to fractures, and can crowd out blood-forming cells in the bone marrow, resulting in low blood cell counts. Myeloma cells produce abnormal antibody fragments that can damage the kidneys, and these fragments can't fight invaders the way normal antibodies do, which leaves people prone to infections.

Treatment for multiple myeloma may include traditional chemotherapy, steroids such as dexamethasone or prednisone, targeted therapies, immunotherapy, radiation therapy and stem cell transplants with high-dose chemotherapy to kill off cancerous blood cells.

The newly approved first-line regimen combines Darzalex, an antibody that targets the CD38 protein commonly expressed on myeloma cells, with three older medications. Velcade is a proteasome inhibitor that kills cancer cells by blocking the breakdown of unneeded proteins. Melphalan is a traditional chemotherapy drug that works by killing fast-growing cells. Prednisone is a corticosteroid that dampens immune responses and reduces inflammation.

For decades, melphalan plus prednisone was the worldwide standard of care for newly diagnosed multiple myeloma, though it is seldom used in the United States. In 2008, researchers showed that adding Velcade increased response rates and extended progression-free survival from 16.6 months to 24.0 months in newly diagnosed patients who are not candidates for stem cell transplants and high-dose chemotherapy, for example older people and those with coexisting

conditions. This three-drug combination is known as VMP.

As reported at the 2017 American Society of Hematology meeting and described in The New England Journal of Medicine, the international ALCYONE trial showed that Darzalex plus VMP reduced the risk of disease progression or death by 50 percent in newly diagnosed people who were considered ineligible for stem cell transplants.

At 18 months, progression-free survival rates were 71.6 percent in the Darzalex plus VMP group versus 50.2 percent in the group randomized to receive VMP alone. The median progression-free survival was 18.1 months for participants taking VMP alone but was not reached in the Darzalex plus VMP group because a majority of participants were still alive and responding.

The overall response rate, meaning complete or partial tumor shrinkage, was 90.9 percent in the Darzalex plus VMP group versus 73.9 percent in the VMP-only group. Complete responses were observed in 42.6 percent versus 24.4 percent, respectively, and 22.3 percent versus 6.2 percent showed no minimal residual disease. The median duration of response was 21.3 months in the VMP-only group and again was not reached in the Darzalex plus VMP group.

The Darzalex combination was generally safe. The most common severe adverse events were neutropenia (low white blood cell count), thrombocytopenia (low platelet level) and anemia, which occurred with similar frequency in both treatment groups. People taking Darzalex were more likely to develop serious infections (23.1 percent versus 14.7 percent), and 27.7 percent had Darzalex infusion reactions, usually mild or moderate.

“A patient’s best chance at lasting remission often begins with a durable response to frontline therapy because multiple myeloma can become more difficult to treat after relapse,” ALCYONE lead investigator Maria-Victoria Mateos, MD, PhD, of University Hospital of Salamanca-IBSAL in Spain said in a Janssen press release. “Combination therapy with daratumumab resulted in deep and durable responses in newly diagnosed patients with multiple myeloma who are transplant ineligible, supporting this regimen as an important new treatment option for these patients.”

Darzalex was already approved for use with Velcade or the immunomodulatory drug Revlimid (lenalidomide) and dexamethasone for multiple myeloma patients who had received at least one prior therapy, with Pomalyst (pomalidomide) and dexamethasone for people previously treated with at least two prior therapies, and as monotherapy for those who had received at least three prior therapies.

The latest approval offers an option for newly diagnosed people starting treatment for the first time who are considered too old or too sick to undergo stem cell transplants. Although experts say this particular regimen with melphalan and prednisone is not likely to change practice in the United States, the results demonstrate the benefits of Darzalex as part of combination therapy for this population, and several other Darzalex-containing regimens are now in clinical trials.

Click here to read a Janssen press release about the Darzalex approval.

Click here to see full prescribing information for Darzalex.
