

Expanded approval for daratumumab in multiple myeloma

In November 2016, the US Food and Drug Administration expanded the approval of daratumumab for patients with multiple myeloma. The monoclonal antibody, which targets CD38, a protein that is highly expressed on the surface of multiple myeloma cells, was previously granted approval by the agency as a single agent for the treatment of patients who had received at least three previous therapies.

The current approval was for the use of daratumumab in two different combination regimens for the treatment of patients who have received one previous line of treatment. On the basis of improved progression-free survival (PFS), demonstrated in two randomized, open-label, phase 3 trials, daratumumab can now be used in combination with the immunomodulatory agent lenalidomide and dexamethasone, or the proteasome inhibitor bortezomib and dexamethasone, both standard therapies for the treatment of multiple myeloma.

In the POLLUX trial, 569 patients with relapsed/refractory multiple myeloma were randomized 1:1 to receive daratumumab in combination with lenalidomide-dexamethasone or lenalidomide-dexamethasone alone. The CASTOR trial randomized 498 patients with relapsed/refractory multiple myeloma 1:1 to daratumumab in combination with bortezomib-dexamethasone, or bortezomib-dexamethasone alone.

The eligibility and exclusion criteria for both trials were similar; patients had received at least one previous line of therapy, had documented progressive disease according to International Myeloma Working Group criteria, and had measurable disease on the basis of urine and/or serum assessments or serum-free, light-chain assay.

Patients with a neutrophil count of $\leq 1,000$ cells/mm³, hemoglobin level of ≤ 7.5 g/dL, platelet count of $< 75,000$ cells/mm³, creatinine clearance of ≤ 20 mL/min per 1.73m² body surface area (or < 30 mL/min in the POLLUX trial), alanine aminotransferase or aspartate aminotransferase level ≥ 2.5 times the upper limit of normal (ULN) range, bilirubin level of ≥ 1.5 or more times the ULN range, disease refractory to bortezomib or lenalidomide, and unacceptable side effects from bortezomib or lenalidomide, were ineligible for these studies. In addition, patients with grade 2 or higher peripheral neuropathy or neuropathic pain, were excluded from the CASTOR study.

What's new, what's important

The expanded approval for the mAb daratumumab in multiple myeloma is for its use in two existing standard combination regimens in patients who have had one previous line of treatment: the first is with lenalidomide plus dexamethasone (POLLUX trial), and the second with bortezomib plus dexamethasone (CASTOR trial). Two randomized, open-label, phase 3 trials had similar inclusion and exclusion criteria, and both showed improved PFS for the addition of daratumumab to the existing combinations (POLLUX: estimated PFS not yet reached vs 18.4 months for lenalidomide plus dexamethasone alone; HR, 0.37; $P < .0001$; 63% reduction in risk of disease progression or death. CASTOR: estimated PFS not yet reached vs 7.2 months for bortezomib plus dexamethasone alone; HR, 0.39; $P < .0001$; 61% reduction in the risk of disease progression/death.)

The most frequently reported AEs were similar in both studies and included infusion reactions, diarrhea, and upper respiratory tract infection, though POLLUX also included nausea, fatigue, and pyrexia, and CASTOR patients also frequently experienced peripheral edema. The most common grade 3/4 AEs in both trials were neutropenia, thrombocytopenia, and anemia. The recommended dose for daratumumab in both combination regimens is 16 mg/kg intravenously, calculated on actual body weight. Neutropenia and thrombocytopenia have been added to the list of warnings and precautions for the new indications. Complete blood cell count should be monitored periodically during treatment and daratumumab administration delayed to allow recovery of neutrophils or platelets. Supportive care with growth factors or transfusion should be considered in the event of neutropenia or thrombocytopenia, respectively.

Jame Abraham, MD, FACP (abrahaj5@ccf.org)

Randomization was stratified according to International Staging System disease stage at the time of screening (stage I, II or III, with higher stage indicating more severe disease), number of previous lines of therapy (1 vs 2, or 3 vs >3), and previous receipt of lenalidomide or bortezomib.

In the CASTOR trial, patients received up to eight 21-day cycles of bortezomib, administered subcutaneously at a dose of 1.3 mg/m² on days 1, 4, 8, and 11 of cycles 1-8, and dexamethasone, administered orally or intravenously at a dose of 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 for a total

Mechanism of action: daratumumab

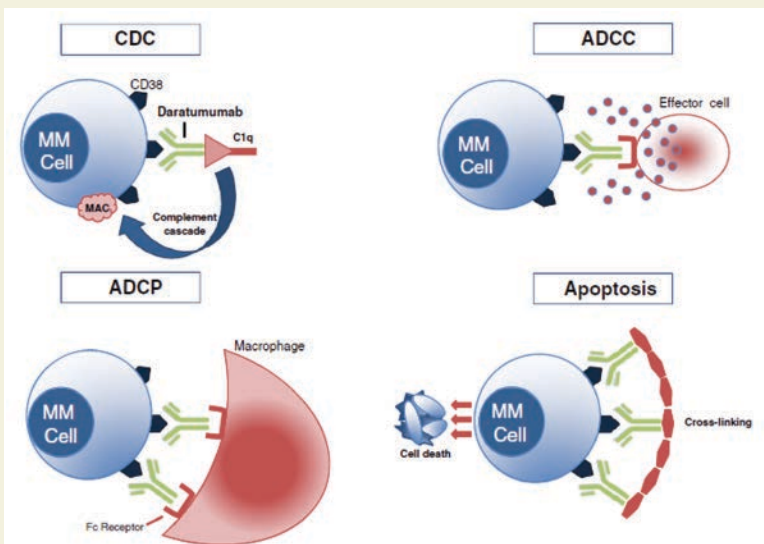
Novel monoclonal antibody, diverse MOAs

Daratumumab is a human immunoglobulin G kappa monoclonal antibody that targets the CD38 protein. CD38 is a glycoprotein and signaling molecule expressed on the surface of numerous immune cells. It has a variety of different cellular functions, including receptor-mediated adhesion, cell signaling, and immune regulation, which are dependent on the type of cell upon which it is located. It is particularly highly expressed on multiple myeloma cells, which has set it apart as a targetable tumor-associated antigen, and this is being exploited by monoclonal antibodies like daratumumab.

Preclinical and clinical studies of daratumumab have revealed it to have a number of different anti-tumor effects, both direct and indirect. It induces multiple myeloma cell death by binding to CD38 located on the cell surface and inducing apoptosis, antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), or antibody-dependent cellular phagocytosis (ADCP).

In addition, it may have an immunomodulatory role that indirectly leads to tumor cell death by fostering an improvement in the anti-tumor immune response. In this respect, studies have shown that daratumumab may drive an increase in the number of helper and cytotoxic T cells and enhance T-cell function and T-cell receptor clonality. Furthermore, a group of regulatory T cells has been found to express CD38 at high levels and daratumumab

treatment may also drive a decline in the number of these cells, which typically have an immunosuppressive effect. Overall, the net effect of daratumumab on the immune response seems to be a shift from immunosuppressive to immune-boosting.



Daratumumab has a diverse array of proposed mechanisms of action, including induction of multiple myeloma cell death through apoptosis, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC).

Reproduced with permission: Sanchez L, Wang Y, Siegel DS, Wang ML. Daratumumab: a first-in-class CD38 monoclonal antibody for the treatment of multiple myeloma. *J Hematol Oncol.* 2016;9:51.

dose of 160 mg per cycle. Daratumumab was administered at a dose of 16 mg/kg intravenously once weekly on days 1, 8, and 15 during cycles 1 to 3, once every 3 weeks on day 1 of cycles 4-8, and once every 4 weeks thereafter.

In the POLLUX trial, patients were treated in 28-day cycles. Daratumumab was administered at the same dose as in the CASTOR trial, but on days 1, 8, 15 and 22 for 8 weeks during cycles 1 and 2, every 2 weeks on days 1 and 15 for 16 weeks during cycles 3 through 7, and every 4 weeks from then onwards. Lenalidomide was administered at a dose of 25 mg orally on days 1-21 of each cycle, and dexamethasone at a dose of 20 mg before infusion and 20 mg the following day.

The combination of daratumumab with lenalidomide-dexamethasone demonstrated a substantial improvement in PFS, compared with lenalidomide-dexamethasone alone (estimated PFS not yet reached vs 18.4 months, respectively; HR, 0.37; $P < .0001$), representing a 63% reduction in the risk of disease progression or death. Meanwhile,

there was a 61% reduction in the risk of disease progression or death for the combination of daratumumab with bortezomib-dexamethasone in the CASTOR trial (estimated PFS not yet reached vs 7.2 months; HR: 0.39; $P < .0001$). The PFS benefit was observed across all prespecified subgroups in both studies.

In the CASTOR trial, over a median follow-up of 7.4 months, the overall response rate (ORR) was 82.9% for the combination arm, compared with 63.2% for the bortezomib-dexamethasone arm ($P < .001$), with a very good partial response (VGPR) or better rate of 59.2% compared with 29.1%, and a complete response (CR) rate of 19.2% compared with 9%. In the POLLUX trial, over a median follow-up of 13.5 months, ORR was 92.9% for the combination arm, compared with 76.4% for lenalidomide-dexamethasone, with a VGPR or better rate of 75.8% versus 44% and a CR rate of 43.1% versus 19.2%.

Overall, the safety profile for both combinations was consistent with what is usually observed with daratu-

mumab monotherapy and lenalidomide-dexamethasone or bortezomib-dexamethasone combinations. The most frequently reported adverse events (AEs) were similar in both studies and included infusion reactions, diarrhea, and upper respiratory tract infection. In the POLLUX trial they also included nausea, fatigue, pyrexia, muscle spasm, cough, and dyspnea, whereas in the CASTOR trial patients also frequently experienced peripheral edema.

The most common grade 3/4 AEs in both trials were neutropenia (51.9% vs 37% in the POLLUX trial and 12.8 vs 4.2% in the CASTOR trial), thrombocytopenia (12.7% vs 13.5% and 45.3% vs 32.9%, respectively), and anemia (12.4% vs 19.6% and 14.4% vs 16%, respectively). The percentage of patients who discontinued treatment due to AEs was similar in both groups across the two studies; in the CASTOR trial discontinuations resulted most commonly from peripheral sensory neuropathy and pneumonia, while in the POLLUX trial, from pneumonia, pulmonary embolism and deterioration in general physical health.

References

1. Darzalex (daratumumab) injection, for intravenous use. Prescribing information. Janssen Biotech Inc. <https://www.darzalexhcp.com/shared/product/darzalex/darzalex-prescribing-information.pdf>. Released November 2016. Accessed January 8, 2017.
2. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:754-766.
3. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:1319-1331.

The recommended dose for daratumumab in both combination regimens is 16 mg/kg intravenously, calculated on actual body weight. The dosing schedules begin with weekly administration during weeks 1-8 (when used in combination with lenalidomide-dexamethasone) and weeks 1-9 (for use with the bortezomib-dexamethasone combination), decreasing to every 2 weeks between weeks 9 and 24 or 10 and 24, respectively, and progressing to every 4 weeks from week 25 onward until disease progression and unacceptable toxicity.

Daratumumab is marketed as Darzalex by Janssen Biotech Inc. Neutropenia and thrombocytopenia have been added to the list of warnings and precautions for the prescribing information for these new indications. Complete blood cell count should be monitored periodically during treatment and daratumumab administration delayed to allow recovery of neutrophils or platelets. Supportive care with growth factors or transfusion should be considered in the event of neutropenia or thrombocytopenia, respectively.