

## Incorporating Monoclonal Antibodies Into the Management of Multiple Myeloma



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### H&O How do monoclonal antibodies work?

**TM** Monoclonal antibodies are immunoglobulins (Igs) that are generated and manufactured to target a specific antigen present on a cancer cell. A monoclonal antibody circulates throughout the body and attaches to cancer cells. Through a variety of immunologic mechanisms, it stimulates the body to fight the cancer. The prototypical monoclonal antibody is rituximab (Rituxan, Genentech/Biogen). Rituximab targets CD20, which is found on most mature B cells. CD20 proved to be a good target for lymphoma therapy, and the use of rituximab has been successful for decades.

### H&O Has the use of monoclonal antibodies in lymphoma informed use in multiple myeloma?

**TM** For several years, many attempts were made to make a monoclonal antibody for multiple myeloma that followed the design of rituximab, which works so well for lymphoma. However, it might have been better to evaluate different types of antibodies for multiple myeloma. There are now antibodies with good activity in multiple myeloma, approximately 25 years after they were identified in lymphoma.

### H&O Is it known why some of the early monoclonal antibodies were not successful in multiple myeloma?

**TM** There are several reasons why a monoclonal antibody may not work for a given cancer. The monoclonal antibody must be able to reach the area where the cancer

cells exist; for multiple myeloma, they are located primarily in the bone marrow. In addition, the cancer cell can neutralize the effect of the monoclonal antibody via multiple mechanisms, such as decreasing the amount of antigen expressed on the surface and increasing the amount of T-regulatory cells in the microenvironment.

### H&O Which monoclonal antibodies are approved for multiple myeloma?

**TM** Daratumumab (Darzalex, Janssen) and elotuzumab (Empliciti, Bristol-Myers Squibb) are approved by the US Food and Drug Administration (FDA) for the treatment of multiple myeloma. Elotuzumab is a monoclonal IgG antibody approved in combination with lenalidomide (Revlimid, Celgene) for patients who have already received 1 to 3 prior lines of therapy. The antigen target of elotuzumab is the signaling lymphocytic activation molecule F7 (SLAMF7), also known as CS1 and CD319. The SLAM group consists of cell-surface glycoproteins that are involved in immune homeostasis. The role of this family group is not completely elucidated. In some circumstances, it appears to enhance the function of natural killer (NK) cells. In other circumstances, it can tamp down the NK cell function. SLAMF7 is almost ubiquitously present on multiple myeloma cells and NK cells. The theoretical mechanism of action is that elotuzumab binds to multiple myeloma cells, acting as a target for immune-mediated destruction, and activates NK cells. The activated NK cells then hone in on the targeted multiple myeloma cells, which eventually leads to the death of the myeloma cells.

Elotuzumab has limited single-agent activity. In a phase 1 study of monotherapy, elotuzumab was associated with a stable disease rate of approximately 20% to 25%. Two larger randomized studies evaluating elotuzumab in combination with lenalidomide and dexamethasone showed positive results for these regimens in terms of response rates and progression-free survival (PFS). In a study that added elotuzumab to bortezomib (Velcade, Takeda) and dexamethasone, an improvement was seen in PFS but not in the response rate.

Daratumumab is a monoclonal IgG human antibody. It targets CD38, which is expressed to a high degree on plasma cells, but is also present on B cells and T cells to a limited degree, as well as on epithelial cells, NK cells, certain monocytes, and red blood cells. Daratumumab was initially approved by the FDA in 2015 for use as a single agent in patients with multiple myeloma who had received 3 or more prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or who were double-refractory to a proteasome inhibitor and an immunomodulatory drug. In a phase 1/2 trial, single-agent daratumumab (16 mg/kg) had a response rate of 36%, with good tolerability.

Based on subsequent data, the FDA approved additional indications in 2016. Daratumumab is approved in combination with lenalidomide and dexamethasone and with bortezomib and dexamethasone for the treatment of patients who have received at least 1 prior therapy. It is also approved in combination with pomalidomide (Pomalyst, Celgene) and dexamethasone for patients who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor.

The clinical data are slightly stronger for daratumumab than elotuzumab. As a single agent, daratumumab is associated with a response rate of approximately 30% to 40%. This response rate is impressive. There are few treatments in multiple myeloma that can match it, plus it was achieved in patients who had received a median of 4 prior lines of therapy (in a study by Lokhorst and colleagues).

Daratumumab also shows a strong response when combined with immunomodulatory imide drugs. The POLLUX trial (A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma) combined daratumumab with lenalidomide. Nearly 600 patients were randomly assigned to treatment with daratumumab, lenalidomide, and dexamethasone or lenalidomide and dexamethasone. Patients in this study had received at least 1 prior line of therapy and were not refractory to lenalidomide. The response rate was 93% for patients treated with daratumumab, lenalidomide, and dexamethasone vs 76% to 80% for

those treated with lenalidomide and dexamethasone. PFS at 18 months was 77% for patients treated with daratumumab vs approximately 50% for those who were not. The hazard ratio for disease progression or death was 0.37; in other words, the addition of daratumumab was associated with a 63% improvement in these clinically relevant outcomes for relapsed myeloma patients. Perhaps even more exciting is that the rate of patients who achieved minimal residual disease negativity was approximately 3 to 5 times higher among patients in the daratumumab arm. Before this trial, it was rare to see patients with multiple myeloma who achieved negative minimal residual disease, especially in the relapsed treatment setting.

Daratumumab also increased response rates when combined with bortezomib. The CASTOR study (Addition of Daratumumab to Combination of Bortezomib and Dexamethasone in Participants With Relapsed or Refractory Multiple Myeloma) compared daratumumab, bortezomib, and dexamethasone vs bortezomib and dexamethasone. The responses were more modest in the CASTOR trial compared with the POLLUX trial, with an overall response rate of 83% for the daratumumab/bortezomib/dexamethasone arm and 63% for the bortezomib/dexamethasone arm. The 12-month PFS was 60% with daratumumab vs 27% in the control arm, and the median PFS was not reached vs 7.2 months, respectively. In patients treated with daratumumab, the risk of progression or death was 61% lower than in the control arm.

The study populations enrolled in the CASTOR and POLLUX trials were different, and the drugs were administered in different ways, which helps with the interpretation of the dissimilar results from these trials. Patients in the CASTOR trial were more heavily pretreated, with 2 median prior lines of therapy vs 1 prior line in the POLLUX study. In the CASTOR study, bortezomib was stopped after 9 cycles, whereas in the POLLUX study, lenalidomide was continued until disease progression. Therefore, patients in the CASTOR study were more heavily pretreated and received less chemotherapy than patients in the POLLUX trial.

These trials of monoclonal antibodies have shown exciting results for patients with relapsed multiple myeloma. As we gain more experience with these drugs, and as they are combined with newer agents, such as carfilzomib (Kyprolis, Amgen) or pomalidomide, the results will likely get even better.

### **H&O** When would you consider initiating treatment with a monoclonal antibody?

**TM** Based on the CASTOR and POLLUX trials,

I consider use of monoclonal antibodies after 1 prior line of therapy, as indicated by the FDA. Responses are better when monoclonal antibodies are administered earlier in the disease course. For example, in the CASTOR study, those patients who had received only 1 previous line of therapy before daratumumab had a 12-month PFS of 77%, vs 44% among those treated with 2 or 3 prior lines of therapy.

### **H&O** What are the advantages of using monoclonal antibodies in patients with multiple myeloma?

**TM** Monoclonal antibodies should not be considered as one drug group because they have differing chemical structures and target different antigens. Daratumumab has been shown to have more activity, in terms of tumor reduction, than elotuzumab. In general, however, an advantage to monoclonal antibodies is that they offer a different modality of treatment. For years, the only treatment for multiple myeloma was alkylating chemotherapy. In the early 2000s, introduction of the immunomodulatory drugs thalidomide and bortezomib was revolutionary. From that time until the advent of the monoclonal antibodies, the new therapies were simply reiterations—albeit refined and more efficacious—of immunomodulatory drugs or proteasome inhibitors.

Lenalidomide is more active than thalidomide, and pomalidomide is more active than lenalidomide. However, lenalidomide and pomalidomide are both based on the same thalidomide backbone. They all bind to the same target, the protein cereblon. Similarly, the proteasome inhibitors all have the same cell target. Bortezomib, the first proteasome inhibitor, drops away from the target after a few hours. The next proteasome inhibitor, carfilzomib, binds to the target irreversibly. More recently, the FDA approved ixazomib (Ninlaro, Takeda) as the first proteasome inhibitor administered orally. Rather than representing huge leaps in drug development, these agents are steps forward.

### **H&O** What are some monoclonal antibodies in development for multiple myeloma?

**TM** There are several monoclonal antibodies in development for multiple myeloma. At the 2016 American Society of Clinical Oncology meeting, Richter and colleagues presented results from a phase 2 trial of single-agent isatuximab. Patients were heavily pretreated, with a median of 5 prior lines of therapy, including lenalidomide, bortezomib, carfilzomib, pomalidomide, and daratumumab. Isatuximab showed good activity, with a response rate of 24%.

Bispecific antibodies attach concurrently to a protein on the multiple myeloma cell surface (eg, CD38) and to the T-cell receptor. They then draw the T cell and the multiple myeloma cell close together, triggering a reaction whereby the T cell kills the multiple myeloma cell. Bispecific antibodies are similar to chimeric antigen receptor (CAR) T-cell therapies, which are being used to treat acute lymphocytic leukemia. In contrast, however, the bispecific antibodies are an off-the-shelf product, whereas the current CAR T-cell therapies are manufactured for each individual patient. Bispecific antibodies can therefore be delivered more quickly. Hopefully, bispecific antibodies will not cause cytokine-release syndrome, at least not to the extent reported with CAR T-cell therapy.

### **H&O** Have new monoclonal antibodies been successful in other types of malignancies?

**TM** There is renewed interest in the use of monoclonal antibody therapy in leukemia, especially with the antibody-drug conjugates, which use a monoclonal antibody to deliver a drug to a cancer cell. In addition, there are monoclonal antibodies that target antigens now recognized to be essential for tumor survival, such as programmed cell death protein 1 (PD-1). In lung cancer, the new monoclonal antibodies nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck) target PD-1.

### **H&O** What toxicities are associated with monoclonal antibodies?

**TM** The primary toxicity is an allergic reaction because these proteins are foreign to the body. The most common reactions are a runny nose or a tickle in the throat. More severe reactions, such as bronchospasm, wheezing, and even full anaphylaxis, are theoretically possible. The toxicity profile of monoclonal antibodies is predictable. Adverse events occur almost exclusively with the first infusion. They can be mitigated through preparation and premedication. In my practice, before initiating treatment with daratumumab, we premedicate with a corticosteroid, a histamine-1 blocker, a histamine-2 blocker, and acetaminophen. We also administer montelukast prior to treatment with daratumumab, based on results from a study my colleagues and I presented at the 2016 American Society of Hematology (ASH) meeting. The rate of infusion reactions decreased from approximately 60% to approximately 40% when montelukast was administered 30 minutes before the infusion of daratumumab. This drop was based primarily on reductions in respiratory or gastrointestinal symptoms.

## H&O Are there any other challenges to the use of monoclonal antibodies in patients with multiple myeloma?

**TM** The administration of monoclonal antibodies requires very long infusions. Infusion of daratumumab can require that patients spend 9 hours in the clinic. This impacts the patient, who may already be tired by the travel involved in coming to and from the clinic. It also impacts the clinic by requiring the use of an infusion chair for the entire day. Various strategies attempt to address this time requirement. In some clinics, daratumumab is administered over 2 days. Sometimes patients are admitted to the hospital for their first dose. An abstract presented at the 2016 ASH meeting evaluated subcutaneous administration of daratumumab via a hyaluronidase-based proprietary mixture that reduces the infusion duration to as short as 30 to 45 minutes. Preliminary data were promising. The time needed for the infusion will likely decrease.

Another major challenge with monoclonal antibodies is that, like all other treatments in multiple myeloma, they are not curative. Patients do progress and relapse after treatment. The question then becomes, what is left for these patients? More therapies are needed.

## H&O How might the use of monoclonal antibodies evolve in these patients?

**TM** It is not yet known. The use of monoclonal antibodies is relatively new in multiple myeloma. In B-cell lymphoma, rituximab is added to nearly every chemotherapy regimen because it tends to enhance the response rate by approximately 10% to 15% and improves PFS. A comparable agent for multiple myeloma is lacking. Data show that the addition of a monoclonal antibody improves outcome with lenalidomide/dexamethasone and bortezomib/dexamethasone, but we do not yet know whether the monoclonal antibodies will combine well with standard 3-drug regimens, such as bortezomib, lenalidomide, and dexamethasone (VRD) or cyclophosphamide, bortezomib, and dexamethasone (CyBORd). We also still lack data showing the efficacy of monoclonal antibodies used in the frontline setting; clinical trials are currently underway to investigate.

In the future, daratumumab or elotuzumab might be added to all regimens until the patient cannot tolerate chemotherapy anymore, at which point daratumumab or

elotuzumab could be used in a maintenance setting (like rituximab in follicular lymphoma). Another approach would be to administer monoclonal antibodies in conjunction with a defined course of chemotherapy. It is difficult at this time to speculate on how monoclonal antibodies will best be used.

### Disclosure

*Dr Mark has received research funding from Celgene, participates in an advisory board for Takeda, and is a consultant for Amgen.*

### Suggested Readings

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